

HALUCINOGENIC AGENTS

HALLUCINOGENIC AGENTS

by

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PREFACE

THE fascination which hallucinogenic drugs have held for man from earliest times continues unabated today. Long used for devout purposes or as sources of divine inspiration, often revered as deities, these drugs now compel the attentions of the hedonist and the scientist. Yet despite two decades of intense scientific investigation there is still no clear understanding of their mode of action, or indeed any agreement as to what constitutes a hallucinogenic effect. This book tries to draw together many of the diverse threads of chemical, biochemical, and pharmacological knowledge of the hallucinogens, in order to put our concept of their action on a firmer basis.

Much of the confusion in the literature is semantic. The names that have been used to describe drugs which produce hallucinogenic effects in man are legionary, exceeded in variety only by the accounts of the hallucinogenic experience. Chapter 1 is a guide through this maze and suggests that 'hallucinogen' is the preferred term for reasons of generally accepted use, despite the fact that not all hallucinogens actually produce hallucinations. It concludes with a description of the sources of hallucinogens, most of which occur naturally in plants and many of which occupy important places in the social and religious lives of the people native to their indigenous areas.

Confusion also arises from the wide variety of pharmacological procedures that have been used to test for hallucinogenic activity. Indeed, one of the major difficulties in this field is to relate what is a psychic and highly subjective response in humans to some measurable effect in animals which may be biologically incapable of experiencing that type of response. Chapter 2 critically reviews the available evaluation procedures, with numerous examples to show their applicability, be it general or particular.

Five chapters are devoted to discussion of individual classes of hallucinogens, based respectively upon phenylalkylamines and their derivatives, indolealkylamines and related compounds, cannabis, drugs affecting cholinergic systems, and finally miscellaneous compounds. The first-named group contains one of the oldest and best-known hallucinogenic drugs, mescaline, which is now to be regarded

as only one member, of relatively low potency, of a series of phenylalkylamines. Recent synthetic developments in our own laboratories and elsewhere have established the existence of compounds such as R(-)-2,5-dimethoxy-4-bromoamphetamine with over 1000 times the potency of mescaline in animals and of others like R(-)-2,5-dimethoxy-4-methylamphetamine with over 150 times its potency in man. Chapter 3 analyses the relationships between hallucinogenic activity and chemical structure in the phenylalkylamine series, including a section on their oxidation products, the adrenochromes.

Indolealkylamines occupy an even older position than mescaline in the history of hallucinogenic drugs, since teonanacatl, one of the four great divinatory drugs of the Aztecs, has a recorded use of at least 3000 years. Both teonanacatl and ololiuqui, of Aztec origin, as well as many of the hallucinogenic beverages and snuffs of South America, contain indolealkylamines such as the tryptamines and the harmala alkaloids. Chapter 4 discusses the origin of these natural hallucinogens together with their more recent synthetic cousins, in particular lysergic acid diethylamide (LSD). LSD is undoubtedly the most potent and most studied of all hallucinogenic drugs, and it would require a book in its own right for complete coverage; in this book, however, we have tried to place it in relation to its simpler structural analogues, the tryptamines.

Relationships between structure and activity become progressively more difficult to discern as one moves from the phenylalkylamines through the indolealkylamines to cannabis, chiefly because of the increasing synthetic problems involved. Moreover, the constitution of crude cannabis extracts was not established until the mid 1960s, and biological work prior to that time is to be regarded with suspicion. Nevertheless, our knowledge of the mode of action of cannabis now increases daily with the continuing investigations of its metabolism and pharmacology. Cannabis is now known to undergo extensive microsomal oxidation *in vivo*, and many of the observed central effects may be due to hydroxylated metabolites of Δ^8 - and Δ^9 -tetrahydrocannabinol. The recent work in this area as well as the effects of cannabis constituents and metabolites in man and experimental animals is the subject of Chapter 5.

Hallucinogens which act principally upon central cholinergic mechanisms are discussed in Chapter 6, including the classic deliriantes such as atropine and hyoscyne as well as newer synthetic drugs like the glycolates and phencyclidine. Discussion of individual groups of drugs is completed in Chapter 7 with a number of compounds which do not fit readily into the previous four categories. These include possibly the oldest hallucinogenic agent, muscimol.

which is derived from the fly agaric mushroom and which may have been the legendary *Soma* of Sanskrit origin.

It is unlikely that all types of hallucinogenic drugs share a common mode of action. At the present state of knowledge it seems reasonable to group the drugs into three categories: the sympathomimetic amines (indolealkylamines and phenylalkylamines); the cannabinoids; the antiacetylcholine drugs; and it is assumed that drugs within these classes act by similar, if not identical, mechanisms. Chapter 8 critically considers the pharmacological and biochemical evidence for this assumption. It stresses the relationship between hallucinogenic effects and interference with neurotransmitter function in the brain, particularly interactions with receptors for 5-hydroxytryptamine, a molecule whose structure closely relates to many of the most potent hallucinogens. The evidence leads to the conclusion that the sympathomimetic amines compete with 5-hydroxytryptamine at its central receptors while the antiacetylcholine drugs compete similarly with acetylcholine. However, both of these classes of drugs give rise to central nervous system excitation, suggesting an inhibitory role for the transmitters with which they are apparently competing, whereas the cannabinoids produce depression of the central nervous system. The effects of hallucinogenic drugs remain as mysterious as the mechanisms by which the body and mind reacts to mediate them.

This book was completed while we were both employed at the Chemical Defence Establishment. We thank the Ministry of Defence for permission to prepare and publish the manuscript.

R. W. B.

R. M. P.

September, 1974.

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Chapter 1

Introduction



I. NOMENCLATURE AND CLASSIFICATION

HALLUCINOGENS represent possibly the oldest known type of drug with effects upon the central nervous system. Many of them have been in use for thousands of years in most civilizations, synthetic drugs of great potency are now available, and the subject has received extensive scientific attention in recent years. Yet today the biochemical, pharmacological, and physiological bases of hallucinogenic action are still not understood and there remains no clear definition or even agreement as to what constitutes such action.

What therefore is hallucinogenic action? Catch 22 readers will readily appreciate the impossibility of responding to this question, since the phenomenon is not directly accessible to the observer while once he partakes of the experience then his objectivity is lost. However, it is unlikely that any rigorously defined concept of 'hallucination' is warranted because 'hallucinogens' as a group produce a kaleidoscope of effects only some of which may be associated with the actions of individual members of that group. This inexactitude has not prevented a proliferation of such definitions, and the volume of the proposed nomenclature is exceeded only by the inventiveness of the protagonists (*Table 1.1*).

Hallucinations have been termed 'non-object-bound sensory phenomena' (Scheibel and Scheibel, 1962) and may include, in addition to simple and complex visual and auditory hallucinations in the classical sense, misperceptions, misidentifications, illusions, paraesthesia, synaesthesia, hypoaesthesia, and eidetic imagery. Such phenomena have been reported by persons ingesting various chemicals and by those suffering psychoses induced by schizophrenia, affective disorders, organic syndromes, or environmental factors. Attempts have been made to identify factors which are constant

Table 1.1.—NAMES USED TO DESCRIBE DRUGS WHICH PRODUCE HALLUCINOGENIC SYMPTOMS*

Name	Introduction
Phantastica	Lewin (1924, 1931)
Hallucinogen	Hoffer, Osmond, and Smythies (1954)
Psychotomimetic	Gerard (1956)
Psychedelic	Osmond (1957)
Psychodysleptic (Dysleptic)	Delay (1959)
Eidetic	Delay (1959)
Pseudohallucinogen	Cohen and Ditman (1963)
Illusinogen	Cohen and Ditman (1963)

*Miscellaneous names used most frequently in the psychiatric literature include euphorgenic, mysticomimetic, phrenotropic, psychehormic, psycheplastic, psycherhexic, psychezymic, psycholytic, psychosomimetic, psychotica, psychotogenic, schizogenic, and schizophrenogenic. Others may be encountered depending upon the whim of those using the term or the particular shade of meaning required.

and common to all hallucinations and thereby to all hallucinogenic drugs (*see*, for example, Klüver, 1966a, b), but it is clear that no two hallucinations are identical whether induced chemically or by psychosis. Classifications of drugs which produce hallucinations have therefore tended to be based more upon other concomitantly observed effects on behaviour and mentation than on the type of hallucination. Unfortunately, these effects are so multifarious as to make precise classification unwieldy although comprehensive compendiums have been compiled (World Health Organization, 1958), and drugs are normally classified according to their most pronounced effects.

The generic term *psychotropic* is now accepted as covering the entire range of drugs which affect the normal working of the central nervous system in one way or another. The father of psychopharmacology, Louis Lewin, devised the first useful classification of psychotropic drugs in his classical book *Phantastica, Narcotic and Stimulating Drugs. Their Use and Abuse*, which appeared originally in German in 1924 with English editions in 1931 and 1964. Lewin defined five classes: (1) *Euphorica*, the mental sedatives, including substances now regarded as narcotics such as morphine, heroin, codeine, and cocaine; (2) *Phantastica*, the drugs of illusion and hallucination, including such substances as peyotl, Indian hemp, and belladonna alkaloids; (3) *Inebrientia*, the drugs characterized by a primary phase of cerebral excitation followed by a state of depression and illustrated by ethanol, diethyl ether, and nitrous oxide; (4) *Hypnotica*, the sleep-inducing agents such as barbiturates, bromides, and the Polynesian kawa beverage; and (5) *Excitantia*, the mental stimulants, including products derived from various

caffeine-containing plants, tobacco, betel, and khat. Thirty years later Hofmann was to use much the same classification for psychotropic drugs although many more substances of synthetic origin were then known to him, but he added a sixth group, the *tranquillizers*, and used the names *analgesics*, *stimulants*, and *psychotomimetics*, for *euphorica*, *excitantia*, and *phantastica* (Hofmann, 1960a).

All the substances to be described in this monograph fall into the *phantastica* subdivision. It is unfortunate that Lewin's designation has not found favour in English-speaking countries since in many ways it is preferable to most of the more complex definitions proposed in subsequent years, none of which is entirely satisfactory. *Hallucinogen* is now the accepted term to replace *phantastica*, and was originally applied to mescaline, lysergic acid diethylamide, and adrenochrome (Hoffer and others, 1954). The term is not ideal since it overemphasizes perceptual changes at the expense of the often more important changes in thought and mood; thus, true visual and auditory hallucinations are not always the most characteristic effects produced by drugs commonly regarded as hallucinogens. The terms *pseudohallucinogen* and *illusinogen* were designed to overcome this semantic difficulty (Cohen and Ditman, 1963), but they have not found widespread popularity and seem to offer little advantage.

Psychotomimetic, originally introduced by Gerard (1956) and which continues to find much favour in the literature, literally means 'psychosis mimicking' and carries with it the unfortunate connotation that such drugs will induce in a normal subject a mental state similar to that which is often present in the true psychoses of many forms of mental illness. Definitions of the term have appeared from time to time from several authors (Osmond, 1957; Hofmann, 1960a; Downing, 1962, 1964; Hoffer and Osmond, 1967) and the consensus is that psychotomimetic agents are substances that will *consistently* produce changes in thought, perception, and mood, occurring alone or in concert, without causing either major disturbances of the autonomic nervous system (for example, clouding of consciousness) or other serious disability (for example, addictive craving). Overdosage may cause disorientation, memory disturbance, hyperexcitation, stupor, and even narcosis, but these reactions are not characteristic. This concept therefore excludes narcotics such as morphine as well as anaesthetics, analgesics, and hypnotics. The true meaning of the word seems to have been lost over the years, and it has been pointed out several times (*see*, for example, Hollister, 1962) that there are well-defined differences between mental states induced by the majority of psychotomimetic drugs and those encountered in mental illness. Moreover, several different types of psychosis are recognized in clinical practice and the drug-induced

model psychosis can hardly resemble all aspects of the various functional psychoses.

Osmond (1957) has introduced the term *psychedelic*, meaning 'mind-manifesting', to convey the fact that the pattern of effects of such compounds is determined not so much by pathological components as by a general activation and manifestation of psychic phenomena which is in no way morbid or negative. The psychedelic drug is said to enrich the mind, to enlarge the vision, and to create a mystic insight, but the term has achieved its maximum use and notoriety in the lay rather than the scientific literature. *Psychodysleptic*, often abbreviated to *dysleptic*, and meaning 'mind-distorting or -disrupting', was introduced by Delay (1959) and is very popular in the French language literature (Radouco-Thomas, Garcin, and Radouco-Thomas, 1969). The latter authors have attempted to classify psychodysleptics on the basis of the type of dependence produced. Thus, analgesics like morphine and heroin produce double (psychological and physiological) dependence while hypnotics and tranquillizers may produce either double or single dependence. The classical hallucinogens like mescaline produce only psychological dependence while cholinergically-mediated hallucinogens such as phencyclidine and atropine do not seem to produce dependence of either type. This classification contributes little to our understanding of hallucinogenic drugs and adds yet more fuel to the fires of semantic confusion. A number of other more exotic names are listed in Table 1.1, but they have no widespread popularity.

In this monograph we will retain the term 'hallucinogen' as a generic name for the whole class of compounds which can produce changes that may be psychotomimetic or psychedelic. We do this not because we are satisfied with the term but in order to avoid perpetuation of the semantic confusion in this field, and we do not imply that hallucinogens always produce hallucinations. They may instead be regarded as chemicals which in non-toxic doses consistently produce changes in perception, in thought, and in mood, but which seldom produce mental confusion and loss of memory. These latter changes are, however, characteristic of a group of pharmacologically active substances termed *hallucinogenic poisons* (Brawley and Duffield, 1972), which induce organic brain syndromes accompanied by hallucinations when given in unusually high doses or in the presence of idiosyncratic sensitivity. Chemically-induced toxic psychoses are beyond the scope of this monograph, since virtually all drugs with effects on the central nervous system will produce them if given in sufficiently high doses. Familiar examples include those due to sulphonamides, tetracyclines, cortisone, thyroxine, phenacetin, ethanol, carbon tetrachloride, household

products like glue and paint solvents, organophosphorus compounds of agricultural and chemical warfare utility, and most of the heavy metals (Hoff, 1967). The hallucinogenic potencies of these compounds apparently depend more upon metabolic disruption of neural and other tissue than upon any discrete neuropharmacological actions.

The first well-defined group of hallucinogens are the *deliriant*s, which characteristically produce a state of confusion, agitation, and dysphoria, together with unpleasant hallucinations, and loss of memory (Abood and Biel, 1962; Gershon, 1966; Abood, 1968; Fink and Itil, 1968). These effects are produced without concomitant metabolic disturbances by drugs of chiefly anticholinergic character; atropine, hyoscine, Ditran, benztropine, trihexyphenidyl, benactyzine, and diethazine are good examples. Many of these drugs are used in the treatment of Parkinson's disease, the therapy of which has long been limited by the poor therapeutic ratio between the beneficial effects of the drugs upon cholinergically-mediated symptoms and their toxic effects (Pinder, 1972).

The *psychotomimetics* are the major class of hallucinogenic drugs and include several families of compounds such as the ergot alkaloids and their synthetic derivatives, indolealkylamines, and compounds derived from phenylethylamine. They typically induce neither delirious states nor general metabolic disturbances and are best known for their hallucinogenic effects (Hofmann, 1968). Though there are differences between the subjective states, potencies, and time-courses of action of these drugs, it is clear that there is a considerable degree of cross-tolerance between them in animals and in man while the most effective antidotes to their action are neuroleptics of the phenothiazine or butyrophenone type. Furthermore, an impressive list of common effects can be compiled which has a constancy acceptable to psychiatrists accustomed to naturally occurring psychopathological disturbances (Hoffer and Osmond, 1967; Brawley and Duffield, 1972). The list includes:

a. *Physiological effects*: mydriasis, elevated heart-rate and blood-pressure, hyperreflexia, tachypnoea, and increased muscle tone.

b. *Sensory effects*: perceptual distortions which progress, with sufficient dosage, through simple and complex hallucinations both visual and auditory.

c. *Psychic effects*: cognitive disturbances such as magical and paranoid thinking, which evolves from the perceptual distortions, accompanied by other elements of formal thought disorder and associative loosening. Affective changes ranging from emotional blunting to elation or extreme excitement, these effects being highly dependent upon the individual subject.

The clear similarities, on chiefly clinical grounds, between individual psychotomimetic drugs and their distinction from deliriants and poisons has led to numerous postulations of a common mode of action for psychotomimetics. This is unjustified in the light of present knowledge because identical phenomenological states may be caused by disparate mechanisms, cross-tolerance may be due not to interaction at a common receptor site but to enzyme induction, while the behavioural antagonism of the neuroleptics may not be due to an agonist-antagonist relationship at the cellular level. Nevertheless, this uncertainty has not prevented attempts to subdivide the class of hallucinogens, or psychodysleptics with only psychological dependence, into two groups according to whether or not they possess stimulatory actions on adrenergic sympathetic structures in the central nervous system (Radouco-Thomas and others, 1969). It is ironic that all of the drugs commonly regarded as hallucinogens seem to have such actions except for the derivatives of tetrahydrocannabinol, the pharmacology of which is largely unknown. The preparations from *Cannabis sativa* produce mixed effects in man, with elements of delirium, euphoria, and hallucination, although they are better known for their euphoriant actions (Keup, 1970; Tart, 1970). Reaction is highly subject and situation dependent, and there appears to be no cross-tolerance between the tetrahydrocannabinols and classical hallucinogens like lysergic acid diethylamide. Chemicals derived from *Cannabis sativa* can therefore be regarded neither as deliriants nor as psychotomimetics, and until their pharmacology is better understood it is safer merely to classify them generally as hallucinogens (Brawley and Duffield, 1972).

II. THE HALLUCINOGENIC EXPERIENCE

It is difficult for anyone lacking personal experience of the strangeness of the psychic changes and abnormal states of consciousness produced by hallucinogens to describe them adequately in words normally used in our daily vocabulary. It is, however, possible to obtain some idea of their nature by a study of the numerous accounts of such experiences written by persons of both artistic and scientific leanings (Huxley, 1954, 1956; Zaehner, 1957; Dunlap, 1961; Newland, 1962; Watts, 1962; Bishop, 1963; Blum, 1964; Cohen, 1964; Leary, Metzner, and Alpert, 1964; Solomon, 1964; Freedman, 1967; Hofmann, 1968).

The underlying changes clearly arise from alterations in the perception of time, space, and corporeity. Time seems to stand still as a result of a compelling immediacy which diminishes the normal importance of past and future. The ability to see familiar objects and events in a new light is another facet of this shift in organized anticipation of time. Forms and colours are changed or assume a new significance, objects lose their symbolic character, and colours become more intense and transparent, radiating from the inside. Awareness becomes intensely vivid while self-control over input is diminished, leading to a lurking threat of loss of inner control and to the 'dying of the ego' so often reported in 'bad trips'. Events take on a trajectory of their own and qualities become more intense with a life of their own; thus, redness is more interesting than the red object, meaningfulness more important than what is meant. The subject leaves the familiar world behind, though without losing consciousness, and enters a pseudo-dream world with different dimensions, time, and standards. There is a split of self and a loss of corporeity, the subject seeming to stand outside himself with a sort of 'spectator ego'. Part of the ego becomes a relatively passive monitor rather than an active, focusing, initiating force, and the other part receives vivid experiences. Visual and auditory hypersensitivity may lead to illusions and hallucinations in which sounds are perceived as colours and vice versa.

In the drug state, customary boundaries become fluid and the familiar assumes novelty and portentousness, but the impairment of goal-directed efficiency is accompanied by impairment of integrative and synthetic functions and abilities. Creativity is unlikely to be increased, therefore, by hallucinogenic drugs since it requires enhancement rather than impairment of synthetic and organizing facilities. The drug may provide new meanings and enhance the need for synthesis, but the characteristic mergings of sensory objects during hallucinosis is not the same as the organized building and arrangement associated with creative processes in which boundaries are essential. Synaesthesia, the plastic rearrangement of objects, and the focusing on details or usually disregarded elements are not the stuff of genius!

III. THE SOURCES OF HALLUCINOGENIC DRUGS

Hallucinogenic drugs now seem an integral and ubiquitous part of European and North American culture, but the origins of their use

Table 1.2.—SOME BOTANICAL SOURCES OF HALLUCINOGENIC SUBSTANCES*

GENUS	SPECIES	COMMON OR NATIVE NAME	CHIEF AREA OF USE†	ACTIVE PRINCIPLES
Moraceae	<i>Cannabis sativa</i> L.	Hashish	Asia, Africa, Europe	Tetrahydrocannabinols
Agaricaceae	<i>Amanita muscaria</i> (Fr.)	Fly agaric, Soma (?)	Siberia, India (?), Europe (?)	Muscimol
	<i>Psilocybe, Conocybe, Stropharia</i> spp.	Teonanacatl	Central America	Psilocin, Psilocybin
	<i>Myristica fragrans</i> <i>Virola</i> spp.	Nutmeg, Mace Yakee, Parica, Epená	Asia, Indonesia South America	Myristicin Tryptamines, Harmine
Cactaceae	<i>Lophophora williamsii</i> (Lem.) Coulter	Peyotl, peyote	Central America	Mescaline
	<i>Anhalonium lewinii</i> Lem. <i>Trichocereus pachanoi</i>	Peyotl San Pedro	Central America Peru	Mescaline Mescaline
Leguminosae	<i>Piptadenia</i> spp.	Cohoba, Yopo	Caribbean, South America	Tryptamines, Harmala alkaloids
	<i>Mimosa hostilis</i>	Vinho de Jurema	South America	Tryptamines, Harmala alkaloids

Table 1.2.—SOME BOTANICAL SOURCES OF HALLUCINOGENIC SUBSTANCES*—*contd.*

GENUS	SPECIES	COMMON OR NATIVE NAME	CHIEF AREA OF USE†	ACTIVE PRINCIPLES
Malpighiaceae	<i>Banisteriopsis</i> spp. <i>Tetrapterys</i> spp.	Caapi Yagé, Ayahuasca	South America	Harmine, Harmaline
Apocynaceae	<i>Tabernanthe iboga</i>	Iboga	West Africa	Ibogaine
Zygophyllaceae	<i>Peganum harmala</i> L.		Africa, Asia	Harmala alkaloids
Piperaceae	<i>Piper methysticum</i> L.	Kava, Kava-kava	Oceania	α -Pyrones
Convolvulaceae	<i>Rivea corymbosa</i> L. <i>Ipomoea violacea</i> L.	Olloliqui, Badoh Badoh negro	Central America Central America	D-Lysergic acid amide and other ergot alkaloids
Solanaceae	<i>Datura stramonium</i> , <i>Atropa belladonna</i> <i>Duboisia Hopwoodii</i> F.	— Pituri	Asia, Europe, North America Australasia	Atropine, Hyoscyne, Scopolamine

*Compiled from Schultes (1966, 1967a, 1969), Farnsworth (1968), and Schultes and Hofmann (1972).

†Prior to modern abuses of the drugs.

lie deep in civilizations of far greater antiquity. Wherever the European has encountered civilizations older than his own he has also encountered the use of psychoactive extracts of plants and fungi—in Asia, in the Americas, and in Polynesia. Synthetic drugs of greater potency are now available, such as lysergic acid diethylamide as a psychotomimetic and esters of glycollic acid as deliriants, but man has known from primitive times how to use various substances from his environment as drugs (Table 1.2). That many of the most potent hallucinogenic preparations from natural sources should come from the New World, particularly Mexico and South America, is probably a reflection of their pattern of distribution rather than for reasons of differences in social and cultural development.

It was rapidly appreciated by primitive man that many natural materials mimicked the ability of certain individuals to attain altered mental states by essentially spiritual means, such as deep involvement in some form of religious experience, or physical means, like asceticism and the complex rituals of Yoga. These drugs were used for medical, social, magical, and religious purposes, and their use and dispensation was a closely-guarded privilege of highly respected members of communities, such as witch doctors or magicians. *Taboos and folk wisdom have tended to guard against excessive use or abuse of hallucinogenic drugs, since members of primitive communities believed that the gods revealed themselves in their own bodies through these agents. That such substances are still used both legally and illicitly on an increasing scale is sufficient indication of man's continuing desire to escape from reality. Sadly, hedonism and nihilism have become the major objectives.

1. DRUGS OF EURASIAN ORIGIN

Undoubtedly the oldest hallucinogenic drug is soma. The plant was introduced into the Indus valley of India by the original Aryans, an Indo-European people of the second millennium B.C. Soma was deified and worshipped, and the more than one thousand hymns written in eulogy of its effects have come down to us intact in Sanskrit texts such as the *Rigveda*. The drug was regarded as a divine inebriant, but in view of the preparation, extraction, and consumption actually occurring during the liturgy it is more likely to have been an hallucinogen than a product of alcoholic fermentation. Its identity has defied definition for many years but Wasson (1967, 1970) has made an authoritative search into the obscure origins of the drug and concludes that it is the fly agaric or *Amanita muscaria*. The documented history of this mushroom goes back only to the

seventeenth century and its use has been confined to the northern reaches of Siberia, although it is common to many parts of Europe and ancient Finnish tribal traditions recall its use (Cheymol, 1969). Wasson believes that the inebriating effects of the fly agaric were known to an Indo-European people in their religious life and that they imparted this practice to the Siberian tribes as well as taking it with them to India. His evidence is mainly linguistic and cultural but makes compelling reading, and fly agaric may come to take its place alongside alcohol, tobacco, and hashish as an outstanding intoxicant of Eurasian man.

The use of hashish, obtained from the hemp plant *Cannabis sativa* L., dates back almost as far as that of soma. Early Chinese civilizations had used the flowering tops of the female hemp plant, which contains the largest amount of pharmacologically active resin, for 'gout, rheumatism, beriberi, malaria, constipation, and absent-mindedness', while Herodotus records that the Scythian tribes living near the Caspian Sea in the fifth century B.C. intoxicated themselves with the vapours of *Κάνναβις* (Solomon, 1968). The consumption of hashish and other preparations of hemp flowers, seeds, and leaves by chewing and smoking spread over a wide area of Africa, Asia, and Europe, and hemp seeds have been found in a German tomb of 500 B.C. Marco Polo returned from his travels with tales of the outlaw band of Hassan Ibn-Sabbah-Homairi (born c. 1056), who were called 'hashishin' and made use of the drug; its properties may have eliminated the fear of battle and probably gave rise to the word 'assassin' (Cheymol, 1969). Though it had undoubtedly appeared in Europe at an earlier stage, hashish did not arouse literary interest until the mid-nineteenth century when a generation of French intellectuals, including Dumas and Balzac, experimented with the drug. Gautier and Baudelaire were the most habitual users, and the latter has provided an excellent description of its effects in his book *Les Paradis Artificiels* (Baudelaire, 1860). More objective descriptions can be found in the work of the French psychiatrist, Moreau de Tours (1845), who used hashish intoxication as a model psychosis to give his students some insight into the world of the mentally ill. Moreau's experiments, which provoked the popular interest in self-administration, are models of the type of clinical studies needed with hallucinogenic drugs while his descriptions of hashish intoxication are little different from those of modern authors.

Self-administration of hashish is now a serious problem in most Western societies, although the use of the drug for social purposes is accepted in many other parts of the world. It can be prepared in many different ways and there are over fifty names by which it is known; bhang, dagga, hashish, kif, and marihuana being the most common

(Watt and Breyer-Brandwijk, 1962). Indian varieties of *Cannabis sativa* L. are particularly rich in the active ingredients and the drug is normally assimilated by smoking the resin, which is excreted from the female inflorescence, in combination with *Nicotiana* leaves. Chewing or swallowing are less prevalent. The drug has always been widely used as an intoxicant in contrast to the predominantly cultic use of hallucinogens, and this, together with the pronounced narcotic component of hashish euphoria, tends to a classification of the drug between the true hallucinogens and the narcotics (Hollister, 1971).

Finally, the deliriant effects of extracts of *Atropa belladonna*, *Hyoscyamus niger*, or *Datura stramonium* have long been known throughout Eurasia and the rest of the world. Their most notorious use was possibly in Ancient Greece, and it is likely that the Delphic oracles were adept in the use of solanaceous intoxication. The drugs, the active principles of which are anticholinergics of the atropine family, were known to ancient Hindu civilizations and were used in Europe for the purposes of witchcraft (Lewin, 1924, 1931) and in North America for intoxication (Der Marderosian, 1968). *Methysticodendron amesianum* is considered by South American Indians to be more potent than *Datura* species in their witchcraft rites, possibly because of its higher content of scopolamine (Farnsworth, 1968). It is also likely that anticholinergics represent the only example of an Australasian source of hallucinogenic drugs, since claims have been made that the aboriginal drug *Pituri* was actually an extract of *Duboisia Hopwoodii* F. which contained hyoscyne (Cheymol, 1969).

2. PACIFIC SOURCES

Two spices, nutmeg and mace, come from the tropical tree *Myristica fragrans*, which is native to the Indonesian and Malayan archipelagos and has been introduced to the Caribbean. Nutmeg has long had applications in folk medicine as a remedy for disorders of the digestive system and as an aphrodisiac, but reports of its use as an intoxicant are comparatively rare (Weil, 1965). It may have been used by early Hindu civilizations and subsequently in various parts of Asia, while there are suggestions that it was taken as a stimulating snuff by natives in remote regions of Indonesia. The most reliable reports are comparatively recent, and nutmeg enjoyed a brief vogue in the nineteenth century as an abortifacient during the course of which its effects on the central nervous system were only too apparent. Scientific descriptions of its effects were due to the English physician William Cullen in 1789 and by the physiologist J. E.

Purkinje in 1829, who both reported spatial and temporal disorientations very similar to those of hashish intoxication (Weil, 1967; Kalbhen, 1971). Similar dramatic descriptions are available for mace, and both spices have found considerable use in recent years as cheap and legally available hallucinogenic drugs.

Kava-kava or kawa is a cloudy khaki-coloured liquid prepared by extraction of the pulverized, grated, or masticated roots of *Piper methysticum*, a plant indigenous to Polynesia and Melanesia (Cronheim, Holmes, and Gajdusek, 1967). The use of kawa is very old and in many areas was connected with the religious cults and ceremonies, and it still forms part of the recognized pattern of social behaviour in many parts of Oceania. In contrast to nutmeg and mace, kawa produces no hangover or unpleasant side-effects although it is much less potent in its action. It apparently produces no more than a mild form of euphoria, described as a happy state of complete comfort and peace with ease of conversation and increased perception, followed by restful sleep. Early European explorers of Oceania, such as James Cook, described the use of kawa, and its already established place in native folklore indicated an extensive history of use. *Piper methysticum* was probably brought from Indonesia by the early inhabitants of Fiji, from where it may have been introduced to Tonga and Samoa. The relative importance of kawa varies widely in Oceania and is primarily a phenomenon of the western cultures of these three island groups (Ford, 1967). Hawaii and Tahiti had the drink at one time but it is no longer consumed in these islands, and it is interesting that the Maori did not drink kawa although the plant is indigenous to New Zealand. The composition of the drink probably varies also, being made from dried roots in Polynesia but from fresh roots in Melanesia; the latter form of kawa is a stronger preparation and rapidly induces deep sleep together with depression in chronic drinkers.

3. SACRED PLANTS OF MEXICO

Among the many wonders that the conquistadors found in Mexico were the four great divinatory drugs of Aztec pharmacology (Del Pozo, 1967). These drugs were used by the priests for religious, magical, and therapeutic purposes and were capable of inducing visions and weird psychic phenomena; they were *piecettl* (related to the common tobacco plant), *peyotl* (a cactus), *teonanacatl* (a mushroom), and *ololiuqui* (a climbing vine). The Aztecs maintained multiple botanical gardens devoted to the cultivation of these and other medicinal plants, which were collected, described, and assayed by sixteenth century chroniclers such as Bernardino de Sahagun and

Francisco Hernandez. The advanced state of botanical knowledge prevailing in Mexican civilizations at this time suggests that such drugs had been in use for many centuries prior to the Spanish conquest. Divine worship and cultic use of plants was tantamount to heresy to the devoutly spiritual missionaries of Catholic Spain, but despite vigorous and extensive measures to suppress their use they have been taken clandestinely throughout the centuries. The native populations considered the drugs to be holy and saw little reason to abandon their drug-induced communion with the gods even after being converted to Christianity. The three hallucinogenic drugs peyotl, teonanacatl, and ololiuqui are still used today for magical purposes by witch doctors in remoter areas of Central America (Hofmann, 1968; Oliver-Bever, 1972).

Peyotl

Use of peyotl in North America was originally limited to only five Indian tribes, but after 1890 it spread over the remaining Indian reservations, including such relatively northern tribes as the Menomini (Slotkin, 1952). The drug now plays an important sacramental role in the rites of the Native American Church, a Christian religious fellowship founded in Oklahoma in 1918. The somewhat bizarre position exists of a legal hallucinogen in the United States which is protected by the Constitution, and the religious use of peyotl has been defended by five distinguished ethnologists when it was erroneously attacked as addictive and morally corrupting by non-Indian Christians (La Barre, MacAllester, Slotkin, Stewart, and Tax, 1951). Peyotl continues to play an important part in the religious lives of the indigenous populations of Central America and the American South-West (La Barre, 1960).

Peyotl was the first of the magical drugs to be analysed and formed the basis of the first scientific studies in the field of hallucinogens. During a trip to Detroit in 1887, Louis Lewin obtained samples of the peyotl cactus from the Parke Davis Company, these 'mescal buttons' being the cut, sliced, and dried parts of the above-ground portion of the cactus. The plant was classified by Hemmings in the Berlin botanical museum as *Anhalonium lewini*, but the name which has prevailed is *Lophophora williamsii* (Lem.) Coulter (Schultes, 1966, 1967a). The cactus grows in the dry northern areas of Mexico and the adjacent south-western states of the U.S.A. A cactus with similar properties, *Trichocereus pachanoi*, also grows in Peru where it has long been used, particularly in the moon rites of the region, as a hallucinogen under the name of *San Pedro* (Schultes, 1967a). Though Lewin was the first to describe the pharmacological effects of peyotl (Lewin, 1888, 1894), the major credit goes to his

contemporary and arch-rival Arthur Heffter (Holmstedt, 1967), who systematically identified the psychoactive principle as mescaline by dint of chemical isolation and self-administration of the different fractions (Heffter, 1896, 1897). Heffter provided the first and classical account of the action of true hallucinogenic drugs as distinct from the euphoric effects produced by hashish, and he experienced spatial and temporal disorientation, vivid colours and imagery, and hallucinations, with both mescaline and the crude peyotl. Thus, in Heffter's first experiment with pure mescaline: 'Violet and green spots appear on the paper during reading. When the eyes are kept shut . . . violet and green spots which are not well defined, then come visions of carpet patterns, ribbed vaulting, etc. From time to time single dots with the most brilliant colours float across . . . Later on landscapes, halls, architectural scenes (e.g., pillars decorated with flowers) also appear . . .' Subsequent classical publications on mescaline intoxication are those of Prentiss and Morgan (1895), Mitchell (1896), Ellis (1898), Klüver (1928, 1966a, b), and Huxley (1954, 1956). However, the prime source of information on mescaline is not available in the English language; Kurt Beringer, a pupil of Lewin, published *Der Meskalinrausch* in 1927 and the book is to mescaline what Moreau's book is to hashish, with clear-cut descriptions of the psychic and somatic symptoms produced by the drug.

Teonanacatl

Teonanacatl can lay claim to being the oldest hallucinogenic preparation. The word translates as 'God's flesh' or 'sacred mushroom' and was mentioned by the Spanish chroniclers of the sixteenth century. Thus, de Sahagun reported that the Indians of Central America ingested the mushroom at both social and religious ceremonies, and it was also used by witch doctors, soothsayers, and priests to endow them with clairvoyant faculties (see Wasson and Wasson, 1957). Nevertheless, Aztec use of teonanacatl is comparatively recent since 'mushroom stones' of great antiquity have been found in Guatemala. These are stone carvings of mushrooms, the stems of which depict the head or entire figure of a god, which appear to be at least 3000 years old. The mushroom cult of Central America suffered somewhat more repression than peyotl and the last remnants seemed to have finally disappeared in 1915 when the American botanist Safford supported the thesis that teonanacatl was merely a synonym for peyotl and that the Spanish chroniclers had confused the dried mescal buttons with mushrooms (Safford, 1915, 1921).

Safford's views were soon to be challenged by reports from several investigators (Schultes, 1937, 1940; Johnson, 1939) during 1936 and

1938. Mushrooms were still being eaten for magical purposes in certain areas of southern Mexico, and final proof came with the Mexican expeditions of the Wassons, who, between 1953 and 1955, took part in several secret mushroom ceremonies and received personal experience of the hallucinogenic effects of *teonanacatl* (Wasson and Wasson, 1957). A further expedition in 1956 allowed the mycologist Roger Heim to identify and classify the most important types of mushrooms used for magical purposes by the Indians. They were foliate mushrooms mostly belonging to the genus *Psilocybe* as well as one species of *Stropharia* and one of *Conocybe* (Heim and Wasson, 1958), and artificial cultivation was effected in Paris of one particular mushroom, *Psilocybe mexicana* Heim. Chemical separation of the active principles, psilocin and psilocybin, was achieved in the Basle laboratories of Sandoz but animal pharmacology of the extracts was equivocal until Albert Hofmann finally ate 32 dried specimens of the mushroom weighing 2.4 g., a medium dose by Indian standards (Hofmann, 1960b, 1968). His previous experience with lysergic acid diethylamide may have prepared him somewhat for what followed, but his descriptions of the hallucinogenic effects are dramatic. Thus, 'Everything assumed a Mexican character . . . I saw only Mexican motifs and colours . . . the doctor supervising the experiment was transformed into an Aztec priest . . . the rush of interior pictures, mostly abstract motifs rapidly changing in shape and colour, reached such an alarming degree that I feared I would be torn into this whirlpool of colour and form and would dissolve'. *Teonanacatl* was thus to provide one of the most potent of the natural hallucinogens, and demonstrated how difficult it is to obtain meaningful results in animals with a drug which produces effects chiefly on the psyche.

Ololiuqui

The third Aztec magical drug, ololiuqui, was to provide even greater surprises for the Sandoz investigators. Hofmann, who had previously discovered the hallucinogenic properties of lysergic acid diethylamide by accidental self-administration and of the related indole psilocybin by deliberate self-administration, identified the psychoactive principles as various simple lysergic acid amides. A synthetic hallucinogenic drug was thereby discovered by accident prior to the identification of closely related chemicals isolated from sources known to man for thousands of years (Hofmann, 1968).

Ololiuqui was certainly known prior to the Spanish conquest and seems to have been even more important in divinity than either peyotl or *teonanacatl*, although its medicinal use may have also been very extensive in the valleys of Mexico (Schultes, 1941). The drug was

used to cure flatulence, to remedy venereal problems, as an analgesic and anti-tumour agent, and was believed to possess a miraculous deity of its own. Francisco Hernandez described and classified ololiuqui between 1570 and 1575. 'A twining herb with thin, green, cordate leaves, slender green stems, and long white flowers. The seed is round and very like coriander. When the priests wanted to commune with the gods they ate this plant to induce a delirium. A thousand visions and satanic hallucinations appeared to them . . .' (Francisco Hernandez, 1651). In spite of Hernandez's good botanical description, ololiuqui provoked as much disagreement as teonacatl, but in 1897 it was finally identified as *Rivea corymbosa*. The plant is known by dozens of names in Mexico and full lists are provided by Schultes (1941) and Hofmann (1968).

The use of ololiuqui persists today in the remote mountains of southern Mexico, where natives of the Zapotec, Chinantec, Mazatec, and Mixtec tribes continue to live in comparative isolation. The drug is normally administered as a potion prepared from the crushed seeds, in water or in native alcoholic beverages (Reko, 1936), and is used by the professional soothsayers ('piuleros') to enhance their advice to clients. Some disagreement arose in scientific circles as to the activity of *Rivea* seeds, since Kinross-Wright (1959) was unable to repeat the generally euphoric reactions described by Osmond (1955). However, Wasson once again obtained authentic samples of two types of ololiuqui from a Zapotec Indian living near Oaxaca; the brown seeds, *badoh*, proved to be *Rivea corymbosa*, while the black seeds, *badoh negro*, were derived from *Ipomoea violacea* L. The mild hallucinogenic properties of ololiuqui were confirmed by the Sandoz investigators, Hofmann again taking the crude extracts himself (Hofmann, 1964). He reported tiredness, apathy, a feeling of mental emptiness and complete meaninglessness of the outside world, together with hypersensitivity to noise and a pleasant feeling of mental and physical exhaustion. The presence of potential hallucinogens in members of the legally available and ubiquitous Morning Glory family has led to considerable cultivation of and experimentation with these plants (Der Marderosian, 1967), although there are no reports of ornamental Morning Glories being hallucinogenic.

4. MAGIC PLANTS OF SOUTH AMERICA

Hallucinogenic preparations derived from plant sources also have a long history of use in South America. They have not, however, assumed such an important role in the social and religious lives of South American civilizations as they have in Mexico. The Andean Indians, including the Incas, have long used the leaves of

Erythroxylon coca for narcotic purposes but the use of hallucinogenic drugs is much less widespread.

Hallucinogenic Snuffs

The most important material used as an intoxicating snuff in South America and the Caribbean was undoubtedly tobacco, and this region boasts a wide variety of containers and implements for the administration and self-administration of snuffs (Wassen, 1965). Tobacco snuffing was a well-established custom in the Caribbean islands long before the arrival of the European, but the natives also snuffed a narcotic, vision-producing powder called *Cohoba*. Thus, the chroniclers of Columbus's second voyage to the Americas recorded that cohoba was used to promote friendliness, convulsive dance rhythms, and for religious purposes. Cohoba was subsequently identified by Safford (1916) as being identical with the *Yopo* snuff of the Orinoco basin of Venezuela and Colombia, both being obtained from seeds of various leguminous plants of the species *Piptadenia* (Schultes, 1967b). Yopo had originally been described in 1801 by Von Humboldt, and his accounts were confirmed 50 years later by the English botanical explorer Richard Spruce. Spruce's work, which was not published until 1908, clearly established the role of yopo as distinctly different from that of tobacco and the snuff was used as an agent for prophesy, clairvoyance, and divination, as well as to induce bravery before battle. Yopo snuffing is now practised by most of the native population of the Orinoco basin, the drug being usually inhaled or blown into the nostrils by means of a forked tube made from chicken bones. A similar snuff called *Vilca* or *Huilca* is used in Peru and is also derived from a plant of the *Piptadenia* species, while the Argentinian snuff *Sebil* may be derived from *Piptadenia colubrina*. Indeed, plants of the genus grow throughout South America from Paraguay and northern Argentina to the Caribbean islands, and it is likely that other hallucinogenic snuffs are being or have been used by the indigenous populations (Altschul, 1967).

The active ingredients of yopo and cohoba have been isolated and identified as various tryptamines, including bufotenine, and N-methyl- and N,N-dimethyl-tryptamines and their 5-methoxy derivatives (Hofmann, 1968). Tryptamines have also been found in the seeds of the leguminous *Mimosa hostilis*, which forms the basis of a magico-religious beverage used by the Pancaru Indians in the Pernambuco area of Brazil under the name of *Vinho de Jurema* (Schultes, 1965). A particularly intoxicating snuff, called *Yakee* or *Paricá*, is used by the witch doctors of several tribes in the Colombian Amazon, the snuff being produced from resin of several *Virola*

species (Schultes, 1954, 1965). *Epená*, which is produced from the bark of *Virola callophyloidea*, is also used as a snuff powder by the Indians of north-west Brazil. These snuffs produce true hallucinations and an exhilarating euphoria, the subjects performing prodigious dancing feats because of a feeling of superhuman quality. Various psychoactive compounds have been isolated from the different snuffs, including the tryptamines found in yopo as well as the indole alkaloids harmine and tetrahydroharmine (Hofmann, 1968). It is interesting that the narcotic beverage *Iboga* of the wet tropical forests of West Africa also contains an indole alkaloid with hallucinogenic properties, ibogaine. Derived from the apocynaceous *Tabernanthe iboga*, ibogaine produces nervous excitement, mental confusion, and a general state of drunkenness, and represents one of the few examples of the use of a hallucinogenic plant preparation in the African continent (Schneider and Sigg, 1957).

Ayahuasca

Harmine and its congeners may also be the psychoactive principles of the South American magic drink known in Ecuador, Peru, and Bolivia as *ayahuasca*, in Colombia as *yagé* and in Brazil and parts of Colombia as *caapi*. These alkaloids are also present in the seeds of *Peganum harmala*, a zygophyllaceous plant native to Central Asia which has been used throughout the Middle East as an intoxicant. The use of *Peganum harmala* is now lost in antiquity although the plant is known on the Indian sub-continent where it can be bought in Mozlem bazaars. However, the drinking of ayahuasca is still widely extended today among the Amerindians of the Amazon region. Kusel (1965) has provided an excellent description of the effects of the drink on both native and white subjects in north-east Peru.

Ayahuasca, caapi, and yagé are prepared from the stem, sometimes together with the leaves, of liana plants of the *Banisteriopsis* species. The material is pounded in a mortar with the addition of water or by boiling pieces of trunk together with its crushed bark; cold water infusions of the rasped bark find use in some areas. *Banisteriopsis caapi* (Spruce ex. Griseb) Morton is used in Brazil, Colombia, and much of Peruvian and Bolivian Amazonia, while *Banisteriopsis quitensis* is used along the Andean foothills. The closely related genus *Tetrapteryx* is also employed in Brazil and Colombia, and the various beverages often contain mixtures of different *Banisteriopsis* and *Tetrapteryx* species together with other additives (Schultes, 1957; Schultes and Raffauf, 1960). The most common additive appears to be *Prestonia amazonica*, particularly to various kinds of yagé, and this plant is known to contain at least one hallucinogenic compound in N,N-dimethyltryptamine (Pinkley, 1969).

The indefatigable Richard Spruce was the first to describe the effects of caapi, during his expedition along the upper Rio Negro in 1852. He reported that the Tukanoan Indians used caapi to induce trances for prophetic and divinatory purposes, which were characterized by frightening visions and colour hallucinations together with feelings of extreme and reckless bravery (Spruce, 1908). In a later visit to the Peruvian Andes foothills, Spruce encountered the Zaparo tribe using the same preparation under the name of 'ayahuasca'. He was pre-empted, however, in publication by Manuel Villavicencio in 1858, who described ayahuasca and its use by several Indian tribes living in Amazonian Ecuador (see Schultes, 1957). The beverage was used for sorcery, witchcraft, prophecy, and divination, and Villavicencio reported that the natives were able to 'foresee and answer accurately in difficult cases, be it to reply opportunely to ambassadors from tribes in a question of war; to decipher plans of the enemy through the medium of this magic drink and take proper steps for attack and defence; to ascertain, when a relative is sick, what sorcerer has put on the hex; to carry out friendly visits to other tribes; to welcome foreign travellers; or, at least, to make sure of the love of womenfolk'. Equally fantastic descriptions of the telepathic qualities of ayahuasca were claimed by a Colombian pharmacist, Rafael Bayon, and are quoted by Reko (1936). Nevertheless, there is considerable discrepancy between the oft-described hallucinogenic effects of such crude extracts and the equivocal effects of pure harmine alkaloids in the laboratory. Clearly, the identity of the psychoactive ingredients of the magic drinks of South America is by no means proven. However, a recent report has apparently confirmed the hallucinogenic properties of ayahuasca (Rivier and Lindgren, 1972). A comprehensive analysis of samples obtained from the Peruvian Amazon revealed the presence of various β -carbolines like harmine, together with 6-methoxytryptamine. The most common additives were rubicaceous plants of the *Psychotria* species, which contain various tryptamines; it is likely that the monoamine oxidase-inhibiting properties of harmine and its congeners allow these tryptamines, not normally effective by mouth, to exert their effects.

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Chapter 2

Evaluation of Hallucinogenic Activity

I. INTRODUCTION

IT will be clear from the remainder of this book that the various classes of hallucinogenic agents produce their effects by a variety of mechanisms of action. The effects themselves, although superficially similar, are certainly not identical for different types of agent or indeed for agents within the same class. It follows that there are no universally acceptable screening methods for detecting hallucinogenic activity in man or in experimental animals. The effects of the drugs in man are, in the main, subjective and reliance has to be placed on the subject himself giving accurate descriptions of his experiences. The experimenter with laboratory animals is in the difficult position of attempting to detect these subjective, often tenuous and indefinite, effects in animals which may not even be capable of experiencing them.

In attempts to overcome these difficulties, indirect or empirical methods have to be used. The indirect approach involves investigating various facets of the pharmacological activity of a hallucinogenic drug or of a series of related drugs. An attempt can then be made to determine whether any aspect of the pharmacology correlates with, or bears any relationship to, hallucinogenic activity. This kind of approach, as well as being of potential value in screening, also has the merit of possibly throwing some light on the mode of action of the drug. In the more empirical approach the procedure is to take a number of hallucinogenic drugs and to determine whether they produce any common effect, usually on some aspect of animal behaviour. New drugs with similar effects, especially if they are related chemically to the known drugs, are likely to be hallucinogenic too.

The aims and objects of workers who are concerned with the evaluation of hallucinogenic drugs in man are somewhat different from those of experimenters with laboratory animals. There will usually be knowledge, or at least suspicion, that the drug has

hallucinogenic properties from previous deliberate or accidental exposure, from the results of studies on animals, or from the fact that chemically-related structures have this sort of activity. The experimenter will be concerned to categorize as accurately as possible the effects of the drug on psychological or psychomotor performance, to compare its effects with those of other hallucinogenic drugs, to determine how closely its effects resemble those seen in natural psychoses, and to establish whether the drug is likely to have any value in the therapy or prophylaxis of mental illness.

The remainder of this chapter will be devoted to an account of some of the methods that have been used to evaluate hallucinogenic activity of drugs in both laboratory animals and in man. It should be pointed out that less work of this kind has been carried out with hallucinogenic drugs than with psychotherapeutic drugs for the obvious reason that the latter confer greater benefits both medically and financially. However, many methods are applicable to both classes of drug. The importance of being able to detect hallucinogenic actions in substances intended for medicinal use in man, or in atmospheric pollutants, industrial solvents, food additives, and other consumer items, is obvious and is now becoming more widely recognized.

II. BEHAVIOURAL AND NEUROPHARMACOLOGICAL STUDIES

There are many reviews of the methods available for behavioural and neuropharmacological studies. Some of these are by Brady (1957), Riley and Spinks (1958a, b), Sidman (1959), Dews and Morse (1961), Hunt (1961), Cook and Kelleher (1962, 1963), Gollub and Brady (1965), and Brimblecombe (1968, 1970a). Most of these reviews are devoted to techniques useful for detecting psychotherapeutic rather than hallucinogenic activity, but the same general principles are applicable to both.

1. STUDIES ON NON-MAMMALIAN SPECIES

A surprising number of non-mammalian species have been tested for their responses to hallucinogenic sympathomimetic amines, that is indolealkylamines and phenylalkylamines. It is difficult to see how results obtained in animals where the nervous system is so differently organized, and often so relatively simple, can be extrapolated to man. Nevertheless, it is of interest that drugs can produce aberrant behaviour even in these species, suggesting that their actions may be on

simple, primitive brain areas rather than on those developed later in evolution.

Christiansen, Baum, and Witt (1962) studied web formation by spiders (*Araneus diadematus* or *A. sericatus*) which had been given mescaline (0.05–5 g./kg.) or psilocybin (0.15–6 g./kg.). Both drugs caused the formation of a shorter thread, with psilocybin being about ten times as potent as mescaline. Witt (1951) also studied the form of webs spun by spiders under the influence of LSD or mescaline. The most striking effect was that the exactitude of the angles in the web was better after LSD ($<0.05 \mu\text{g.}$) than after mescaline. The study concluded on this evidence that the effect of the two drugs in man was likely to be due to different mechanisms of action. The justification for this considerable extrapolation is difficult to support.

Mansour (1957) showed that rhythmical activity of the liver-fluke (*Fasciola hepatica*) was stimulated by both LSD and 5-hydroxytryptamine. The effect, which appeared to be peripheral in that it was not mediated through the central ganglion, was antagonized by dopamine as well as by the hallucinogenic drugs yohimbine, harmine, and 2-bromo-LSD. The behaviour of the salamander (*Triturus viridescens*) was shown by Peters and Vanderahe (1956) to be modified by LSD; mystery snails (*Ambalaria cuprina*) were also reported to respond to the drug with typical persistent disorganized movements (Abramson and Jarvik, 1955). The effects of 2-bromo-LSD were quite different in that the animals responded by shutting their opercula and remaining immobile.

Among vertebrates, fish have been widely used, especially for their responses to LSD. Most workers used the Siamese fighting fish, *Betta splendens*, which respond to concentrations of 1–5 $\mu\text{g./ml.}$ of LSD in their water with autonomic, motor, and behavioural disturbances (Abramson and Evans, 1954; Smith and Moody, 1956; Arbit, 1957). Characteristically, the fish rose to the surface and assumed a nose-up, tail-down position. Abramson's group further demonstrated that low concentrations of potassium cyanide or sodium azide in the water, or lack of oxygen, produced similar behaviour in the fish (Abramson, Weiss, and Baron, 1958). These authors suggested that LSD might act by poisoning certain oxidative enzymes and went on to speculate that schizophrenia resulted from similar malfunction of respiratory enzymes in man.

There are a few reports of the effects of drugs other than LSD on Siamese fighting fish. Thus, various ergot derivatives were compared with LSD but were found not to produce the characteristic effects. LSD appears to be unique, since mescaline, which produces similar effects in man, has relatively little activity in the fish (Evans, Geronimus, Kornetsky, and Abramson, 1956). There is some

disagreement in the literature over the effects of antagonistic drugs to this LSD response. Smith and Moody (1956) failed to show any effect of azacyclonol, chlorpromazine, or reserpine given before, during, or after LSD administration. Turner (1956), however, claimed that azacyclonol reduced the intensity and duration of the response.

Other fish have been used including carp. Abramson, Gettner, Hewitt, and Dean (1961) force-fed some 1800 assorted compounds to this species and reported that only LSD and closely-related compounds produced characteristic surfacing behaviour. Saxena, Bhattacharya, and Mukerji (1962) reported work with *Colisa lalia* in which individual males were kept separate, thus inducing fighting behaviour when another male was introduced into their tank. Injected doses of mescaline (0.1–0.3 μ g. per fish) produced a phase of excitation followed by a phase of slowed activity. The response towards an intruder gradually became less marked. The same doses of LSD caused the fish to move to the surface of the water and to float there horizontally, but the introduction of an intruder fish evoked a very marked response. The skin pigmentation of the fish became more marked in response to LSD, an effect which has also been reported in guppies. Cerletti and Berde (1955), using *Poecilia reticulatus*, and Berde and Cerletti (1957), using *Lebistes reticulatus*, reported that LSD caused an expansion of the melanin-containing chromatophores in the skin of these fish. Prior administration of 5-hydroxytryptamine prevented this effect.

Studies on birds have been mainly confined to the pigeon, a species much used in operant conditioning experiments where they can be trained to peck at a lever in order to obtain a food reward. A typical study was by Blough (1957), who showed that doses of 0.2 mg./kg. of LSD increased the response rate of pigeons and also improved their accuracy of response. Other drugs were effective in reducing both accuracy and rate of response, such as chlorpromazine (30 mg./kg.) and meperidine (30 mg./kg.), while pentobarbitol (10 mg./kg.) caused a more marked but less persistent reduction in accuracy and rate. Caffeine (10 mg./kg.) had no effect on accuracy but caused a slight increase in response rate. This study is of particular interest because it shows clearly differing patterns of activity resulting from drugs with different types of central action.

2. BEHAVIOURAL STUDIES IN MAMMALS

There are many reports in the literature of the effects of hallucinogenic drugs on mammalian behaviour. No attempt will be made here to give a detailed account of all these studies. Many are isolated pieces of work with individual drugs, difficult to relate to other

studies, and hence their value in predicting hallucinogenic activity is impossible to assess. This account will concentrate in the main on a few investigations in which substantial numbers of drugs have been used to determine whether any common pattern of activity emerged.

Behavioural studies can be broadly classified as either observational or instrumental, that is the animals can simply be observed for the appearance of certain patterns and aspects of behaviour, or some kind of apparatus can be used to measure and often to evoke particular behavioural responses of the animal.

Observational Methods: Sympathomimetic Amines

It is certainly not possible by simple observation of any animal to say definitely that it has received a hallucinogenic agent. Some animals, especially cats, dogs, and monkeys, exhibit behavioural effects which suggest that they are hallucinating, but it is not possible to make an objective assessment of a subjective phenomenon like hallucinations. However, some apparently characteristic responses to hallucinogenic drugs have been reported. Maffii and Soncin (1958), using mice, showed that mescaline in intraperitoneal doses of 10–30 mg./kg. induced intense paroxysms of scratching activity in the animals, which were also hypersensitive to stimuli such as touching and handling. It was possible to distinguish this stereotyped response to mescaline from other characteristic responses to amphetamine, caffeine, morphine, or nicotine. The mescaline response was partially or completely blocked by meprobamate, mephenesin, phenobarbitone, and chlorpromazine; morphine potentiated the response but atropine was without effect. The scratching response to mescaline was also studied by Deegan and Cook (1958), who reported that it could be antagonized by chlorpromazine and other phenothiazines as well as by 5-hydroxytryptamine, reserpine, hydroxyzine, azacyclonol, and mephenesin. In contrast to the findings of Maffii and Soncin, Deegan and Cook could detect no antagonistic actions of barbiturates. Intracerebral injection of small doses (10–50 μ g.) of mescaline produced similar paroxysms of scratching, as did 10–30 μ g. of 5-hydroxytryptamine given by the same route. Kulkarni (1973) has also recently described the dose-related scratching response of mice to several 2,5-dimethoxylated amphetamines, and it is interesting that his ranks of potency are similar to those obtained with other behavioural responses in small mammals or in man.

It seems possible that this stereotyped scratching behaviour is related to the 'head-twitch' in mice, first reported by Corne, Pickering, and Warner (1963) to occur after injection of 5-hydroxytryptamine and more recently claimed by Corne and Pickering (1967) to be

produced characteristically following administration of hallucinogens of all types. This claim, if substantiated, would allow use of the method as a screening test, for as well as appearing to be reasonably specific for hallucinogenic drugs it was also claimed to give some prediction of the possible hallucinogenic dose in man. Corne and Pickering postulated that the response is due to a liberation of 5-hydroxytryptamine in certain parts of the brain. If this is so then it is a most important finding, opening new avenues of research into the mode of action of hallucinogenic drugs. In the author's own laboratories, the head-twitch test has been used with only limited success; the response certainly seems to occur following a variety of hallucinogenic drugs, but attempts to quantitate the response and to obtain dose-response relationships for comparative assays have not been successful.

One of the most complete studies of observed behaviour was described by Norton (1957) and Norton and Tamburro (1958). Cats, hamsters, and monkeys were scored for sociability, contentment, excitement, and defensive and aggressive hostility, before and after drug treatment. Mescaline and LSD had similar effects on cats, which showed decreases in contentment and sociability with increases in excitement and aggressive and defensive hostility. The pattern in hamsters was rather different, with no change in contentment or excitement but increases in sociability and defensive and aggressive hostility.

Tests of this kind are probably of most value when experienced observers are available. Whether relatively inexperienced observers can be relied upon to detect some of the more subtle aspects of behaviour is open to question. In an attempt to overcome this difficulty some workers have chosen to observe animals in a circumscribed environment for a relatively small number of behavioural effects. Brimblecombe (1963) used an open-field test to study the effects of a number of hallucinogenic drugs on the behaviour of rats. The test situation, first described by Hall (1934), comprises an open arena into which a naive rat is placed. This evokes a stereotyped pattern of behaviour characterized by exploration, rearing, preening, and emotional urination and defaecation. Various types of centrally active drugs modify this basic pattern of behaviour in different ways. Brimblecombe showed that several hallucinogenic drugs had a common effect, that of reducing the amount and frequency of emotional defaecation. Unfortunately, the ratio between the effective dose in this respect and the hallucinogenic dose in man was not constant for all the drugs studied.

Woolley (1955) reported an interesting effect of LSD in mice. He observed that when the animals were placed on the edge of a sheet of

glass which was raised to form an inclined plane they braced themselves to avoid sliding and looked apprehensively from side to side. Intraperitoneal injection of about 4 mg./kg. of LSD induced a similar pattern of behaviour in mice on a level surface, and Woolley suggested that the drug produced hallucinations of sliding down an inclined plane. It was possible in some animals to prevent this response to LSD by the intracerebral injection of 1 mg./kg. of 5-hydroxytryptamine together with either 4 µg./kg. of carbamoylcholine or 40 µg./kg. of physostigmine.

Using rhesus monkeys, Evarts (1956) made a careful comparative study of the effects of bufotenine (5 mg./kg.) and LSD (1 mg./kg.). The animals were tested for muscle power, deep tendon reflexes, locomotion, and responses to various stimuli. Both drugs produced gross sensory disorders with ataxia and visual disturbances but no marked defect in muscle power. The monkeys were markedly more tense than normal.

In many studies drugs have been administered intracerebrally rather than by systemic routes. These experiments might be expected to give information about drug activity uncomplicated by such factors as binding to tissue proteins, detoxication, and difficulty of penetration into the central nervous system. Haley (1956, 1957) using mice found that 5 µg. LSD produced aggressive, hyperactive behaviour followed by a period of lethargy. Mescaline at 10 µg./kg. also increased aggressiveness and induced paroxysms of scratching similar to those seen following systemic administration of the same drug. Again this was succeeded by a period of hypoactivity.

Drugs have also been administered to cats and dogs by intracerebral injection. Haley (1956) showed that doses of 1–10 µg./kg. of LSD injected into the third ventricle of unanaesthetized dogs produced whining and shaking of the head followed by salivation, ataxia, retching, emesis, micturation, and tachypnoea. Later the pupils, although reactive to light, were dilated. The animals appeared frightened and tended to revert from adult behaviour patterns to puppy ones. Similar effects of LSD on cats were reported by Haley and Gupta (1958), but Sturtevant and Drill (1956) found only sedative effects after intracerebral injection of 5–100 µg. of the drug to cats. This sedation, they claimed, could be differentiated from natural sleep, from the tranquillity produced by reserpine, 5-hydroxytryptamine, or chlorpromazine, and from the catatonic stupor produced by mescaline. Schwarz, Wakim, Bickford, and Lichtenheld (1956) also described this catatonic stupor after mescaline administration to cats, and stated that similar effects were produced by adrenochrome and adrenolutin. LSD, on the other hand, produced a hyperactive state. Rice and McColl (1960)

reported aggressive behaviour in cats after intracerebral mescaline or adrenochrome.

Injection of drugs has also been made directly into localized areas of solid brain tissue of cats rather than into ventricles (Wood, Stone, and Seager, 1958). LSD injected into the region of the ventromedial nucleus of the hypothalamus produced a depressed, quiet, and unresponsive state. In contrast, reserpine or 5-hydroxy-tryptamine injected into this region caused an increase in activity with vocalization.

Interactions between hallucinogenic drugs and other types of drug have been studied. Burton, Sodd, and Goldin (1957) found that LSD, as well as *d*-amphetamine and *d*-desoxyephedrine, reversed, or at least interrupted, reserpine-induced sedation in mice. Other lysergic acid derivatives were rather less effective than LSD in this respect, or were totally ineffective. In particular, the weakly-hallucinogenic 2-bromo-LSD had no effect. The same authors showed that LSD had only a slight effect on chlorpromazine-sedated mice and no effect on the duration of pentobarbital-induced anaesthesia. Brown (1957) demonstrated that LSD antagonized the actions of 5-hydroxytryptamine and reserpine in causing prolongation of hexobarbital-induced anaesthesia in mice.

Observational Methods: Other Drugs

Very much less work has been done with the effects of other hallucinogenic drugs on observed behaviour. Anti-acetylcholine drugs produce excitation with hypermotility; this will be referred to in more detail in the next section of this chapter dealing with instrumental methods. Cannabis extracts and both naturally-occurring and synthetic cannabinoids all produce clear-cut central nervous system depression (*see* Chapter 5), although there are some reports (for example, Barry and Kubena, 1969) of small doses producing an initial period of excitation.

Observational Methods: General Comments

It is clear from what has been written that no observational method will unequivocally detect hallucinogenic activity. Signs of excitation alone are not diagnostic since they are also produced by non-hallucinogenic stimulants of the central nervous system, for example, caffeine or amphetamine. In any case hallucinogenic cannabinoids produce depression rather than excitation. Perhaps the most promising test is the 'head-twitch' procedure of Corne and Pickering (1967), but before this can be properly evaluated it must be used by other groups of workers and applied to a wider range of hallucinogenic drugs. The same comment applies to the open-field test described by Brimblecombe (1963).

Instrumental Methods: Sympathomimetic Amines

Most animals indulge in a certain amount of non-directed spontaneous activity, particularly when they are introduced into a new environment. This spontaneous motor activity is relatively easy to measure with simple apparatus and is often modified by centrally-acting drugs. Central nervous system stimulants increase activity while central nervous system depressants have the reverse effect.

Brown (1957), using photocell activity cages, showed that intraperitoneal doses of 28 and 80 mg./kg. of LSD produced a four-fold increase in the spontaneous activity of mice, the effect persisting for 3-4 hours. These doses are, however, enormous even allowing for the fact that rodents appear to be relatively insensitive to the behavioural effects of LSD. Taeschler and Cerletti (1957) also reported this excitatory effect of LSD to mice but found that the weakly-hallucinogenic drug 2-bromo-LSD had no such action. Reserpine potentiated the effect of LSD; Tripod (1957) also showed that mescaline increased the spontaneous activity of mice.

Other studies involving simple pieces of apparatus are those in which the time taken by animals to climb a pole or a rope has been used as a criterion of activity. Smythies (1959), using mice, showed that doses of 1-2 mg./kg. of LSD increased the time taken to climb a pole. Bufotenine and adrenochrome in doses up to 20 mg./kg. had no effect, while adrenolutin, at 20 mg./kg., was also without effect itself but inhibited the action of LSD. The morpholide derivative of lysergic acid was less active than LSD but caused a delayed accelerant action on the climbing time. Earlier, Freedman, Aghajanian, Ornitz, and Rosner (1958) had shown that a small dose (130 µg./kg.) of LSD increased the median climbing time of rats in a rope-climbing test. Animals injected daily with this dose of the drug had developed a complete tolerance by the fourth day. Mescaline (10 mg./kg.) also lengthened rope-climbing time but the development of tolerance was slower. These apparently depressant actions on climbing behaviour are perhaps surprising in view of the general excitation produced by the drugs.

Other workers using similar test procedures have studied the interactions between hallucinogenic and other types of drug. Mahler and Humoller (1959) made a careful comparative study of the effects of LSD and bufotenine on pole-climbing time in rats. Both drugs prolonged climbing times, minimal effective intraperitoneal doses being 0.3 and 8 mg./kg. respectively. Tolerance to the effects of both drugs was seen and the effects were potentiated by prior injection of reserpine, 5-hydroxytryptamine, or iproniazid. It was suggested that the potentiation was due to elevated brain 5-hydroxytryptamine levels and that both drugs acted by similar

mechanisms in producing hallucinogenic effects. This is discussed in more detail in Chapter 8. It is significant that Winter and Flataker (1956), also using a rope-climbing technique with rats, found, contrary to Mahler and Humoller, that both 5-hydroxytryptamine and its precursor amino-acid 5-hydroxytryptophan antagonized the action of LSD (0.5 mg./kg.) in prolonging climbing time. Their result with reserpine, an intensification of the LSD effect, was in agreement with the finding of Mahler and Humoller.

Freedman and Aghajanian (1959) made the interesting observation that rats tolerant to LSD were also tolerant to mescaline, in rope-climbing tests. This tolerance was, however, 'one-way' since animals tolerant to mescaline showed an enhanced response to LSD. The point was also made that this finding did not hold for all the behavioural and autonomic effects of the drugs.

Very many studies have been made of the effects of psychoactive drugs on conditioned avoidance responses in animals. Two methods are commonly used. The first is based on an apparatus first described by Cook and Weidley (1957) in which rats are placed in a box with a grid floor. The refuge is a wooden pole attached to the roof of the box. The conditioned stimulus is a buzzer and animals which respond to this within a given time period by climbing onto the pole avoid an electric shock which is otherwise applied to the feet through the grid floor. The second type of apparatus is a shuttle-box in which animals are similarly conditioned to avoid a shock by passing from one half of the two-compartment box into the other half. Both types of apparatus can be used to study the effects of drugs on the acquisition of the conditioned avoidance response, on the ability of an animal already conditioned to reproduce the response, or on the extinction of the response, that is the rate at which it is lost when no longer reinforced by electric shock. A variety of psychoactive drugs has been shown to block conditioned avoidance responses so that this effect is in no way diagnostic of the type of action of a particular drug. The technique has, however, proved useful for ranking members of series of drugs in order of potency and for studying interactions between drugs.

Herz in 1960 reviewed the effects of drugs on conditioned avoidance responses. Most workers prior to that time had agreed that both LSD and bufotenine blocked responses but that mescaline was without effect even when large doses were used. More recently Satory, Pfeifer, and Vizi (1964) have demonstrated that doses of 3-10 mg./kg. of *N,N*-diethyltryptamine inhibit a jump response in rats. Using a shuttlebox, Chorover (1961) showed that 25 mg./kg. of mescaline given intraperitoneally to rats suppressed the conditioned avoidance response. This is in contrast to earlier findings and

appeared to be genuinely a blockade of the conditioned, rather than the unconditioned, response, since the animals showed no signs of physical incapacitation and their orienting responses to the conditioned stimulus suggested that they still heard the buzzer. Gessner and Page (1962), also using a shuttle-box, made a thorough study of the effects of various *N*-alkyltryptamines and LSD on rats. Next to LSD, 5-methoxy-*N,N*-dimethyltryptamine was the most active compound in abolishing the conditioned avoidance response, the doses required to produce comparable effects being 1.85 and 3.7 mg/kg. respectively. *N,N*-Dimethyltryptamine (4.7 mg./kg.) and *N,N*-diethyltryptamine (6 mg./kg.) were also effective, but bufotenine and 5-benzyloxy-*N,N*-dimethyltryptamine showed little activity.

Key (1961a, b) conditioned cats to cross a barrier in response to auditory stimulation. LSD (15–20 µg./kg.) decreased the rate of extinction of conditioned avoidance response. Later, Key (1964) carried out similar experiments with cats using a visual stimulus and found that LSD caused a decrease in response time. When the animals were distracted by a series of tonal pips presented simultaneously with the visual conditioning stimulus there was a lengthening of response time which was increased still further by LSD. The conclusion to be drawn from these experiments seems to be that under the influence of LSD the cats found difficulty in discriminating between significant and non-significant stimuli. This matter is discussed in greater detail in Chapter 8. If this effect of LSD is shared by other hallucinogenic agents it might form the basis of a very useful test for this type of activity.

An effect possibly related to that reported by Key in cats was that demonstrated by Ansfield and Johnson (1961), who trained normal and blind rats to run a maze. Blind animals under the influence of doses of 0.1–0.25 mg./kg. of LSD took a longer time to run the maze and made more errors than normally-sighted rats given the same doses of drug. It seemed that the animals which learned and ran the maze using cues other than visual ones were more severely affected by LSD, that is the effects of the drug were lessened by the presence of visual cues.

Another large body of literature is concerned with the effect of hallucinogenic drugs on animals in operant conditioning situations, that is where the reinforcement is positive and the animals work for a reward rather than to avoid a punishment. Experiments can be designed in a great variety of ways using schedules of reinforcement described in the classical work by Ferster and Skinner (1957). Oakley and Marrazzi (1961) found that LSD (0.1 mg./kg., i.p.) increased the latency of rats trained to press a lever for a water

reward when a tone signified that water was available. Chlorpromazine, in a dose (0.03 mg./kg.) which had no effect itself, partially antagonized the effect of LSD. In a more complicated situation where the rat is required to discriminate between two signals to obtain its reward upon pressing the lever, Marrazzi (1961) found that LSD (0.01 mg./kg.), mescaline (10 mg./kg.), and amphetamine (0.75 mg./kg.) had little effect on the correctness of the response.

Appel and Freedman (1965) trained rats to press a lever for a food reward using a schedule which meant that the animals had, eventually, to press the lever 30 times before being rewarded. The drugs studied were the *d*- and *l*-forms of LSD, 2-bromo-LSD, psilocybin, mescaline, and *d*-amphetamine. All caused decreases in response rate but their potencies varied. *d*-LSD at a dose of 0.13 mg./kg reduced the rate of responding to about 55 per cent of normal while 1.04 mg./kg. resulted in virtually complete cessation of lever pressing. The *l*-isomer of LSD, 2-bromo-LSD, psilocybin, and amphetamine were all about one-tenth as potent as *d*-LSD. Mescaline was the least potent; a dose of 10 mg./kg. was required to produce an approximately equivalent effect to *d*-LSD. As well as these quantitative differences there were some qualitative differences between the effects of the drugs, but, as the authors emphasize, the procedure is sensitive to psychoactive drugs with different actions and fails to discriminate between classes of compounds. It is certainly not specific for hallucinogenic drugs.

Monkeys, too, have been used. Jarvik and Chorover (1958) trained these animals to obtain a sweetened liquid reward in a situation requiring a delayed response. Doses of LSD as low as 0.05 mg./kg. caused a decrease in the accuracy of the response while higher doses tended to depress the rate of performance. Tolerance to the effects of LSD soon developed and persisted for several days. In comparison, amphetamine, pentobarbital, and chlorpromazine only produced changes in accuracy of responding at dose levels where the rate of pressing was markedly reduced.

This account of a few studies of the actions of hallucinogenic drugs of the sympathomimetic amine type on animals using instrumental methods will suffice to show the range of techniques and the variety of results obtained. Again it is clear that none of these procedures can unequivocally detect hallucinogenic activity even within this somewhat circumscribed class of agents. Some of the methods are useful for comparing potencies within series of analogues but once more it is exceedingly difficult to form any accurate assessment of the usefulness of the techniques since in none of the studies undertaken have large numbers of compounds been used.

Instrumental Methods: Cannabis

Many early workers with cannabis used either a corneal anaesthesia test in rabbits or a dog ataxia test. It is highly unlikely that either of these tests is relevant to the hallucinogenic activity of the drugs. Similarly, the peripheral pharmacological actions referred to in Chapter 5, notably those on the cardiovascular system, are of little relevance in this context. It is possible that the analgesic and hypothermic actions of cannabinoids, being presumably central in origin, may form the basis of techniques for evaluating hallucinogenic activity but very much more work is required before this can be established.

The use of instrumental methods has, almost without exception, demonstrated central depressant actions of cannabinoids. Thus, there are a number of reports of dose-dependent depression of responses in rats and pigeons in operant conditioning situations by both Δ^8 - and Δ^9 -tetrahydrocannabinol (Black, Woods, and Domino, 1970; Frankenheim, McMillan, and Harris, 1970, 1971; McMillan, Harris, Frankenheim, and Kennedy, 1970). In conditioned avoidance response situations cannabinoids have been repeatedly shown to block the response. Δ^9 -THC had this effect on rats in a shuttle-box (Grunfeld and Edery, 1969), while Domino, Hardman, and Seevers (1971) reported that the synthetic cannabinoid DMHP (see Chapter 5) at a dose of 10 mg./kg. selectively reduced avoidance behaviour of rats in a pole-jump situation of the type described by Cook and Weidley (1957). Domino and his colleagues further showed that the dog is especially useful for screening the pharmacological effects of cannabis extracts and accordingly they developed a test in which dogs were trained to perform foreleg flexion in response to an auditory stimulus so as to avoid an electric shock. Intravenous doses of 0.25 mg./kg. of DMHP resulted in about a 75 per cent reduction in avoidance behaviour. Escape behaviour was reduced to a lesser extent, again showing the selectivity of the effect. The effects of DMHP on shuttle-box avoidance behaviour in monkeys were also studied. In two out of three animals an intravenous dose of 0.5 mg./kg. of DMHP completely blocked avoidance responses while only about 50 per cent of the escape responses were blocked. It was concluded that the animals were in a confusional state.

These examples serve to show that cannabinoids disrupt conditioned responses in a number of animals. The effect on avoidance behaviour is relatively specific, with the escape response being less affected. However, many other psychoactive non-hallucinogenic drugs have a similar selective effect.

Instrumental Methods: Antiacetylcholine Drugs

A characteristic effect of centrally-active, and therefore hallucinogenic, antiacetylcholine drugs is to produce increases in spontaneous motor activity in rats and other rodents. This has been reported by a number of workers (Harris, 1961; Abood, 1968; Brimblecombe and Buxton, 1972). The last authors studied eight drugs and were able to show a correlation between their potencies in producing hyperactivity and in blocking oxotremorine-induced tremors in mice. The implication of this finding, which is discussed in greater detail in Chapter 8, is that the drugs are acting centrally as antagonists of acetylcholine to produce their particular behavioural response. Whether this response bears any relation to the hallucinogenic activity of the drugs is open to question since there is at present insufficient information regarding their potencies in the human species.

Antiacetylcholine drugs have also been widely studied for their effects on the acquisition or retention of a variety of responses, both conditioned and spontaneous. The drugs typically block these responses, seemingly interfering with processes involved in learning or memory. These effects are presumably related to the production of amnesia in man.

A number of workers have investigated the actions of the drugs on spontaneous alternations, which is the behaviour characteristic of rats placed in a simple T-maze of entering opposite limbs of the T on successive trials. Since the direction taken in any run is influenced by the previous run it seems clear that memory is involved. Meyers and Domino (1964) found that both hyoscine (0.13 or 1.05 mg./kg.) and *l*-hyoscyamine (1.0 or 8.0 mg./kg.) caused a reduction in spontaneous alternation. Parkes (1965) found that a dose of 0.1 mg./kg. of hyoscine caused a significant interference with the effect in 50 per cent of the trials. Doses of atropine of 2–5 mg./kg. were required to produce similar effects, reflecting the relative lack of central activity of the latter drug. Burřs (1968) used basically the same system but punished non-correct, that is non-alternating, responses with electric shock. A dose of 6 mg./kg. of atropine clearly impaired the alternation response. The same animals were used repeatedly in this series of experiments and so became progressively overtrained. Presumably because of this their response to atropine became less marked.

There have been many studies of the effects of antiacetylcholine drugs on conditioned responses. The results of many, but not all, of them indicate that the drugs have an amnesic effect. Longo in 1966 reviewed 20 reports of the effects of atropine and hyoscine on discrete trial avoidance, mainly in rats. In half of the studies, the

drugs had no effect on performance, in 3 there were increments, and in 7 decrements of performance. Longo noted that decrements were most likely to be seen when the conditioned response was either recently acquired or involved complex motor performance. Other factors to be taken into consideration must include the dose used, the route of administration, and the interval between giving the drug and testing the animals. Similar apparent inconsistencies have been found in discrimination avoidance studies and in operant conditioning situations.

One difficulty in interpreting the results of conditioning studies arises from the hyperactivity produced in the animals by the drugs. This could easily give rise to effects which might be interpreted as increments in performance. Thus, Brimblecombe and Buxton (1972) tested eight antiacetylcholine drugs for their effects on the acquisition of a conditioned avoidance response in rats in a shuttle-box and for their potency in increasing spontaneous activity in the same species. The results were not easy to interpret but it appeared that increased numbers of avoidances shown by animals given three of the drugs were not due entirely to their hyperactivity. This conclusion is supported by the work of Oliverio (1967), who studied the effects of hyoscine on avoidance conditioning of mice in a shuttle-box. He found that the drug enhanced performance in naive animals but disrupted it in animals which had already acquired the conditioned response.

This very brief survey will suffice to show that instrumental methods demonstrate a variety of central actions of antiacetylcholine drugs, but until more information is available concerning the hallucinogenic activities of these drugs in man the predictive nature of the methods is impossible to assess.

3. NEUROPHARMACOLOGICAL STUDIES IN MAMMALS

Basically there are two approaches to the study of the effects of drugs on the electrical activity of the brain. Recordings can be made of spontaneous electrical activity at cortical or subcortical sites, or stimuli can be applied and the resulting potentials evoked in appropriate sensory areas can be recorded.

Sympathomimetic Amines

Evarts (1957) reviewed the neurophysiological effects of some hallucinogenic agents. The drugs used were LSD, mescaline, N-allylnormorphine, adrenochrome, and marihuana. Information on the latter three drugs was scanty but all of them had a tendency to increase the percentage of slow waves in the electroencephalogram

(E.E.G.) of man and various experimental animals. Mescaline was claimed, at least by some workers, to produce effects similar to LSD which had been much studied prior to 1957 and which was generally agreed to produce a pattern of high-frequency, low-amplitude waves characteristically associated with alert behaviour.

Subsequent work has tended to confirm these early observations. Thus, Speck (1958) reported that mescaline (5 mg./kg., i.p.) increased low-voltage, fast activity in the E.E.G. of the rat, and Monnier and Tissot (1958), using rabbits, showed that LSD produced a state of arousal with generalized desynchronization in the E.E.G. (that is, fast activity). Monroe and Heath (1961) used monkeys with electrodes chronically implanted in various brain regions and studied the effects of mescaline and LSD, as well as various derivatives thereof. All the active drugs produced disturbed, catatonic-like or agitated behaviour, which was associated with paroxysmal, hypersynchronous electrical activity in rhinencephalic regions.

Bradley and Key (1958) made the important observation that in cat *encéphale isolé* preparations, that is with the spinal cord sectioned at C₁, LSD unlike amphetamine did not produce the pattern of fast activity in the E.E.G. Reference is made further to this experiment in Chapter 8 in connexion with the mode of action of LSD, as it is to the finding of Key (1964) that doses of LSD (10–15 µg./kg., i.p.) made cats increasingly responsive to stimuli so that sleep activity (that is the E.E.G. pattern of high-amplitude, low-frequency waves) was recorded only with difficulty. In these animals a greater number of stimuli was required before habituation occurred. Horovitz, Mulroy, Waldron, and Leaf (1965) used cats and rats with chronically implanted electrodes in the lateral hypothalamus and on various cortical areas. The animals were able to operate a lever which caused self-stimulation via the lateral hypothalamus electrode; other animals responded for a food reward. LSD at doses of 10–15 µg./kg. produced the typical cortical E.E.G. pattern of low-amplitude, high-frequency activity in cats and an increase in their rate of response. Rats were less susceptible, with doses of 5–40 µg./kg. causing no change in their response rate.

Baran and Longo (1965) reported that a number of hallucinogenic drugs administered intravenously to rabbits resulted in a disappearance of theta activity (4–7 Hz) from the E.E.G. The drugs were tryptamine 1–2 mg./kg., N,N-dimethyltryptamine 0.5–1.0 mg./kg., bufotenine 2–3 mg./kg., psilocybin 1–2 mg./kg., and mescaline 50–75 mg./kg. Lower doses of all the drugs affected the behaviour of the rabbits. All the drugs had effects similar in many respects to those of LSD, but dissimilar from effects seen after administration

of non-hallucinogenic sympathomimetic amines, analeptics, and convulsants. The drugs, however, flattened the E.E.G. less markedly and less consistently than LSD.

These few examples serve to show that a variety of hallucinogenic agents of the indolealkylamine and phenylalkylamine type evoke changes in the pattern of spontaneous electrical activity of the brain, there being a general tendency for the E.E.G. to be desynchronized, that is to show a pattern characterized by fast, low-voltage activity.

There have also been studies of the effects of hallucinogenic sympathomimetic amines on averaged evoked responses. Brawley and Duffield (1972) point out that this is not a very satisfactory way of investigating sensory function since the waveforms of the responses vary among species, individuals, and laboratories, and also because the physiological interpretation of the components of the response is not straightforward. A further point is that the form of evoked cortical responses varies with the background electrocortical activity at any given time. The available evidence is summarized by Brawley and Duffield. It shows that LSD and other sympathomimetic hallucinogens can have both facilitatory and inhibitory effects on evoked responses depending on the sensory modality, the species, the exact circumstances of the experiment, and other factors. These effects are not specific for hallucinogens, however, and many of them can be reproduced by other drugs. In the face of this confusion it can be concluded with Brawley and Duffield that 'averaged evoked response data offer little insight into the mode of action of psychotomimetics'. Neither do they offer any potential for developing a screening or evaluation procedure for such drugs.

Finally, there have been studies on the limbic system which is concerned with affect, attention, and perception, all of which are modified by hallucinogens. One piece of evidence of apparent significance is the finding that LSD has no behavioural effects in monkeys following temporal lobectomy (Baldwin, Lewis, and Frost, 1957). There are also several reports of modifications in the electrical activity recorded from various parts of the limbic system in animals given hallucinogenic drugs. Thus, Schwarz, Sem-Jacobsen, and Petersen (1956) reported that administration of either LSD or mescaline resulted in slow-wave (2-7 Hz) activity in the temporal lobe. Rhythms of similar frequency (3-10 Hz) were also reported in the amygdala, supraoptic nucleus of the hypothalamus, dorso-medial nucleus of the thalamus, caudate, midbrain reticular formation, and hippocampus of cats with chronically implanted electrodes after a number of hallucinogenic phenylalkylamines (Fairchild, Alles, Jenden, and Mickey, 1967). The activity recorded from

cortical areas in these animals was of the low-amplitude, high-frequency type. Amphetamine caused the latter type of activity in both cortical and subcortical areas. This may form the basis of a test for distinguishing between hallucinogenic and non-hallucinogenic drugs in the phenylalkylamine series.

Antiacetylcholine Drugs

Centrally-acting, and therefore hallucinogenic, antiacetylcholine drugs have a characteristic effect on electrocortical activity of the brain. It was reported by Wikler in 1952 that dogs given atropine could display excitement while exhibiting E.E.G. patterns normally associated with sleep. It has since been demonstrated that other antiacetylcholine drugs have similar effects and the phenomenon has come to be referred to as a 'dissociation' between behaviour and electrocortical activity. Bradley (1958) showed that this dissociation occurred in cat *encéphale isolé* preparations (with the spinal cord sectioned at C₁) but not in *cerveau isolé* preparations (with the mid-brain transected at the intercollicular level leaving the cerebral hemispheres isolated from the brain-stem). It appears, therefore, that the antiacetylcholine drugs act on some system rostral to the reticular formation. Jasper (1961) suggested that the diffusely projecting thalamic system might be involved. There was some doubt as to whether the dissociation effect was due to antiacetylcholine activity, but Brimblecombe and Green (1967, 1968) were able to show a statistically significant degree of correlation between central antiacetylcholine potencies of a number of drugs and their potencies in producing this dissociation. The behavioural significance of dissociation is still not clear, but if it bears a relationship to hallucinogenic activity of the drugs in man then it follows that a simple procedure for predicting hallucinogenic potency of a drug in man would be to measure its central potency in antagonizing acetylcholine. The procedure is discussed in more detail later in this chapter.

There has been at least one study, by Green and Aldous (1972), of the effects of antiacetylcholine drugs on evoked potentials in cats. Atropine, hyoscine, and N-methyl-3-piperidylbenzilate were used; in contrast to LSD these drugs reduced the degree of fluctuation in the amplitude of auditory evoked potentials recorded from the lateral lemniscus under distractive conditions, that is they appeared to reduce the attentiveness of the animals. Like chlorpromazine, the antiacetylcholine drugs disrupted a conditioned avoidance response of the cats and caused an increase in peak latency of the surface positive secondary potential evoked in the auditory cortex. The latter effect may well reflect a decrease in significance or meaningfulness of the stimulus.

Cannabis

The most complete study of the neuropharmacological effects of a cannabinoid is that by Domino and others (1971), using the synthetic compound DMHP. It seems almost certain that the effects of this compound are typical of those produced by cannabinoids in general. For details reference should be made to the original paper, but in summary the findings were that there was a very clear correlation between brain electrical activity and gross behavioural effects of the drug, that is behavioural depression was accompanied by high-voltage slow-wave E.E.G. activity in cortical and subcortical areas. The drug appeared not to impair motor output unless very large doses were given, and although there was some distortion of sensory input the probable mechanism of action of the drug in blocking conditioned avoidance responses seemed to be on higher brain functions resulting from a confusional or depressed state. It is unlikely at present that neuropharmacological techniques will be useful for the specific diagnosis of cannabis-like activity.

III. OTHER PHARMACOLOGICAL EFFECTS

The difficulties inherent in carrying out and interpreting the results of behavioural and electrophysiological studies are considerable. It is not surprising, therefore, that there have been attempts to ascertain whether any more easily measured pharmacological action of hallucinogenic drugs can be related to their activity in producing aberrant behaviour.

1. SYMPATHOMIMETIC AMINES

It has been known for some time that small doses of LSD cause elevations in the body temperature in a number of species of animals. Horita and Dille (1955) reported that rabbits were the most susceptible species, a finding confirmed subsequently by many other workers. They found that cervical spinal section abolished the effect, as did administration of tubocurarine or pentobarbital; morphine augmented the effect. The indications were that the effect originated centrally, a conclusion supported by Supek and Milković (1955) and Cerletti (1955). Rothlin, Cerletti, Konzett, Schalch, and Taeschler (1956) postulated that a centrally-induced 'sympathicotonia', of which the elevated body temperature was only one manifestation, might play an important role in causing the hallucinogenic effects of LSD. Then in 1957, Neuhold, Taeschler, and Cerletti

showed that LSD still caused the hyperthermia in rabbits after removal of the cerebral cortex, suggesting a subcortical site of action, probably the diencephalon. Horita and Gogerty (1958) found that administration of 5-hydroxytryptophan (5-HTP), the precursor of 5-hydroxytryptamine (5-HT), to rabbits also resulted in a hyperthermic response and that the response, whether due to LSD or to 5-HTP, was potentiated by the monoamine oxidase inhibitor, iproniazid. This led to the suggestion that 5-HT was directly responsible for the effect, and further support was provided by Elder and Shellenberg (1962) for this view.

The question arises as to whether this hyperthermic response has any value as a screening test for predicting hallucinogenic activity in LSD-like compounds. Hofmann in 1960 reported results with 18 derivatives of lysergic acid. The psychotomimetic or hallucinogenic potencies of these drugs in man were compared with their potencies in producing a central 'stimulation syndrome' as manifested by their activities in causing hyperthermia in rabbits. Broadly speaking there was a parallelism between these two activities of the drugs whereas their anti-5-HT activities did not parallel their hallucinogenic activities.

Later, Brimblecombe, Downing, Green, and Hunt (1964) reported that a series of tryptamine derivatives was effective in producing hyperthermia in rabbits and, although no exact correlation between this effect and psychic activity in man was possible because of lack of human data, all the compounds known to show activity in man also produced hyperthermia in rabbits. Subsequently, Brimblecombe (1967) measured the hyperthermic activity of a larger series of tryptamines and showed a good correlation between this activity and activity in influencing the behaviour of rats in an open-field situation. As a result of this work the suggestion was made that hallucinogenic tryptamines act on the same receptors in the central nervous system as does LSD and that the behavioural changes in the open-field test and the hyperthermia are both part of the resulting syndrome. Recently, in the authors' own laboratories, a large series of amphetamines and related phenylalkylamines have been tested for their hyperthermic activity. Comparisons between their effectiveness in this respect and their published effectiveness in producing aberrant behaviour in man tend to strengthen the view that this hyperthermic response in rabbits gives a reliable prediction of hallucinogenic activity in man of indolealkylamines and phenylalkylamines. Nevertheless, non-hallucinogenic compounds of these types also cause hyperthermia and it is always necessary to confirm the psychotomimetic nature of the hyperthermia by further behavioural and neuropharmacological studies.

2. ANTIACETYLCHOLINE DRUGS

It was suggested earlier in this chapter that a simple, and probably reliable, procedure for predicting hallucinogenic potency in this class of drugs would be to measure their central antiacetylcholine potency. The method of choice, described by Brimblecombe and Inch (1970), Brimblecombe, Green, Inch, and Thompson (1971), and Brimblecombe, Inch, Wetherell, and Williams (1971), and described and reviewed by Inch and Brimblecombe (1973), is to test the ability of the drugs to antagonize oxotremorine-induced tremors in mice.

Oxotremorine is a muscarinic agonist which produces all the signs of peripheral parasympathetic activity in experimental animals but also produces marked muscular tremors which are central in origin and which appear to result from the interaction of oxotremorine with central muscarinic receptors (Bebbington and Brimblecombe, 1965; Brimblecombe, 1970b). There is as yet insufficient evidence concerning the hallucinogenic activities in man of drugs of this type to enable firm conclusions to be drawn concerning the predictive value of the oxotremorine antagonism test, but where data exist they do seem to confirm its validity. For example, estimates of the hallucinogenic dose of atropine in man lie between 30 and 50 mg.; for hyoscine the dose is between 0.8 and 4 mg. (White, Rinaldi, and Himwich, 1956; Miller, 1956; Ostfeld and Araguette, 1962)—that is hyoscine is probably some twenty times as potent as atropine. The potency of hyoscine relative to atropine in the oxotremorine test is 14.7 (Brimblecombe and Green, 1968). Abood, Ostfeld, and Biel (1959) reported that *N*-methyl-3-piperidyl phenyl glycollate was twice as potent as the *N*-ethyl ester in producing psychotomimetic effects in human subjects. Brimblecombe and Green (1968) found that in the oxotremorine test the ratio of potency of the two drugs was 1.5:1.

It can be concluded that a drug with classical antiacetylcholine activity (for example, ability to antagonize the effects of acetylcholine on isolated guinea-pig ileum) and the ability to antagonize oxotremorine-induced tremors will be a hallucinogen. Its hallucinogenic potency will probably be related to its potency in the oxotremorine test.

3. CANNABIS

At the present state of knowledge there is no relatively simple pharmacological procedure which can be used to detect a cannabinoid type of hallucinogenic activity.

IV. BIOCHEMICAL EFFECTS

The view that hallucinogenic drugs may produce their effects by modifying aminergic mechanisms within the brain is explored in more detail in Chapter 8. The question arises as to whether changes in brain amine levels following drug administration can be used to detect hallucinogenic activity. Leonard (1972) described results of studies which showed that the hallucinogenic drugs LSD, mescaline, Ditran, and phencyclidine, all caused elevations in brain 5-HT, due apparently to a reduction in its turnover, and decreases in brain noradrenaline, due apparently to an increase in turnover rate. Stimulant amphetamines, in contrast, caused elevation in levels of brain noradrenaline, at least when administered in low doses. It is too early to say whether these biochemical changes are specifically diagnostic of hallucinogenic effects. The doses of drugs required to produce them are high and do not appear to bear any fixed ratio to the hallucinogenic doses in man. More work in this area is required.

V. HUMAN STUDIES

The scientific, semi-popular, and popular literature abound with accounts of the effects of hallucinogenic drugs on man. Many of the accounts describe self-experiments and, even if the subject is experienced and familiar with psychological terminology, they are of necessity entirely subjective in nature. Much more valuable from the point of view of the scientific evaluation of hallucinogenic drugs are studies in which objective observations have been made of groups of subjects and where, preferably, the effects of more than one drug have been compared. It is probably true to say that the majority of the latter type of studies have been carried out at the Addiction Research Centre at Lexington, Kentucky. Reference has been made to a number of human studies in the chapters of this book dealing with specific types of drug. A few more will be described here, particularly some of the earlier ones carried out in the late 1950s and early 1960s when investigations of hallucinogenic drugs were being carried out intensively.

* As in the case of animal experiments LSD has been studied more than any other drug. Its effects were first experienced by Hofmann in Switzerland in the 1940s and since that time it has been taken by very large numbers of allegedly normal subjects and psychiatric patients with a variety of mental conditions. Its effects have been described in detail by, for example, Hoffer and Osmond (1967) and Shepherd, Lader, and Rodnight (1968). A typical study was by

Berzel, Travis, Olinger, and Dreikurs (1956), who used 25 'presumably normal' volunteers and gave them oral doses of LSD ranging from 30 μ g. to 100 μ g. Autonomic effects including dilatation of the pupil, increased perspiration, feeling of general warmth, and nausea occurred in many of the subjects, but the intensity of these effects did not seem to be dose-dependent. Dimaxio, Greenblatt, and Hyde (1957) recorded heart-rate, respiration, skin temperature, blood-pressure, and muscle tension, and also reported a general sympathetic excitation. There is general agreement in the literature that these autonomic or somatic effects constitute the initial phase of the reaction to LSD and its derivatives as well as to mescaline, psilocybin, and probably to all hallucinogenic phenylalkylamines and indolealkylamines.

The second phase of the LSD reaction, well described by Jacobsen (1963) and by Hoffer and Osmond (1967), is one dominated by sensory and emotional disturbances. Changes can occur in any of the senses and may be simply a distortion of sensation, or a sensing of non-existent phenomena, or hallucinations. The last-named when they occur are almost always visual. Catell (1954) claimed that after mescaline the hallucinations were specific to the individual subject in the sense that they could be related to his personality in terms of the contained pictures. The emotional effects are normally manifested as changes in mood. Euphoria is commonly experienced although this may be preceded or followed by depression. The majority of subjects retain insight into their condition during the experience and have almost complete recall subsequently.

Certain effects of LSD seem to be dose-related but not others. Thus, Abramson, Jarvik, and Hirsch (1955) studied the effects of the drug on 31 normal subjects using doses of 0, 1-25, 26-50, 51-75, 76-100, and over 100 μ g. The symptoms were classified as either psychotic (confusion, depersonalization, hallucinations, etc.) or neurotic (anxiety, increase in heart-rate, feelings of warmth or cold, etc.). There was a highly significant degree of correlation between dose and occurrence of psychotic effects, but none between dose and neurotic effects. The latter, it was suggested, were more related to the personality of the subject and to the conditions of the experiment. De Maar, Williams, Miller, and Pfeiffer (1960) showed a relationship between dose and the number of symptoms experienced by a group of subjects. The same subjects were able to distinguish between the effects of 25, 50, and 100 μ g. doses of the drug.

Attempts to relate responses to LSD to various factors in the subjects given the drug have not led to any clear relationships being demonstrated. The effects on the response of the subject's environment during the drug experience have also been studied.

Some of the more interesting experiments have been with subjects in a situation of sensory deprivation. Results, for example by Cohen and Edwards (1964), suggest that effects are not nearly so marked in such an environment in contrast to those obtained in experiments with, for example, blind animals where the effects were more marked (Ansfield and Johnson, 1961).

Many psychological and psychomotor tests have been used to test the LSD response. Jarvik, Abramson, Hirsch, and Ewald (1955) found that 100 μ g. of the drug impaired the ability of subjects to do arithmetic but that 50 μ g. was without effect in this respect. Silverstein and Klee (1958) observed that the ability to memorize a series of digits was impaired by doses of 100–150 μ g., and there is general agreement that lower doses (75–100 μ g.) disrupt performance in a variety of psychological tests. Examples of such studies are those by Abramson, Jarvik, Hirsch, and Ewald (1955) and Aronson and Klee (1960).

Studies in which the effects of LSD have been compared with those of other drugs include that by Isbell, Miner, and Logan (1959a). These workers gave the drug and various of its congeners to male Negro prisoners. They measured knee-jerk thresholds, blood-pressures, and pupillary diameters at intervals after drug administration as well as carrying out mental examinations and requiring the subjects to complete a questionnaire. All the modifications to the LSD molecule, with the exception of acetylation of the indolic nitrogen (to give *d*-1-acetyllysergic acid diethylamide) resulted in a reduction in hallucinogenic activity. There was no correlation between the potency of the drugs in antagonizing 5-HT *in vitro* and their hallucinogenic activity, and it was concluded by the authors that the results did not support the hypothesis that LSD produced its effects by creating a relative deficiency of the neurotransmitter in the brain.

This conclusion is supported by the findings of many workers that mescaline and psilocybin, which are not potent inhibitors of 5-HT *in vitro*, produce very similar effects to LSD in man. Isbell, in 1959, reported that a number of subjects could not distinguish between the effects of LSD and psilocybin, and he suggested that the drugs were acting by a common biochemical mechanism. This view is supported by cross-tolerance studies. Wolbach, Isbell, and Miner (1962) compared the effects of LSD (0.75 μ g./kg. and 1.5 μ g./kg.) with mescaline (2.5 and 5 mg./kg.) given to the same 10 subjects. Both drugs caused dilatation of the pupils, elevation of pulse-rate, increase in body temperature, and increase in systolic blood-pressure. They also both decreased the threshold of the knee-jerk reflex. The mental changes resulting from the two drugs were also similar, being

characterized by anxiety, difficulty in thinking, mood changes (usually to euphoria), altered sensory perception (especially visual), visual hallucinations, and alterations in body image. Subjects receiving either drug daily became tolerant to its effects and cross-tolerant to the effects of the other drug. Earlier, Isbell, Wolbach, Wikler, and Miner (1961) had shown that cross-tolerance exists between LSD and psilocybin. Balestrieri and Fontanari (1959) also demonstrated a cross-tolerance between LSD and mescaline in man, but claimed that prolonged administration of 2-bromo-LSD did not cause resistance to the effects of LSD. This is contrary to the findings of Isbell, Miner, and Logan (1959b) who pretreated 10 subjects with 3 mg. of 2-bromo-LSD daily for 5 days and found a statistically significant reduction in the intensity of the response to LSD in these subjects. A rather surprising finding was that of Rosenberg, Isbell, Miner, and Logan (1964), who showed a resemblance between the effects of LSD and *N,N*-dimethyltryptamine in human subjects but were able to demonstrate only a mild degree of cross-tolerance between the drugs.

There have been a number of studies, mainly by Hungarian workers, on the effects of some *N*-alkyltryptamines on man. Böszörményi and Szára (1958) investigated *N,N*-dimethyltryptamine and suggested that schizophrenics were less sensitive to the effects of 1 mg./kg. of the drug than were other subjects. Böszörményi, Der, and Nagy (1959) compared the effects of *N,N*-dimethyltryptamine with those of its close analogue *N,N*-diethyltryptamine. The effects of the former drug (0.7–1.0 mg./kg.) lasted for 50–60 minutes and were characterized by intense autonomic effects, anxiety, disturbances of mood and perception, alterations in perception of time and space, etc. The effects of *N,N*-diethyltryptamine (0.7–0.8 mg./kg.) were longer lasting, persisting for some three hours and were qualitatively different; after subsidence of initial unpleasant autonomic effects, a meditative, pleasant, and euphoric mood developed. The ability to concentrate was lost and there was a disturbance of the perception of space, time, and body image. Changes in the E.E.G. seemed to resemble those produced by mescaline and LSD. Similar differences in response to closely-related tryptamine derivatives were reported by Murphree, Dippy, Jenney, and Pfeiffer (1961). They studied α -methyl- and α -ethyltryptamine on penitentiary inmates with previous experience of LSD. Doses of 20 mg. of α -methyltryptamine and 150 mg. of α -ethyltryptamine were used, the former drug causing some increase in blood-pressure and the latter a significant slowing in heart-rate. Both drugs caused dilatation of the pupils. The effects of α -ethyltryptamine appeared within $\frac{1}{2}$ –1 $\frac{1}{2}$ hours, while those of its homologue took 3–4 hours to appear.

The majority of subjects who received α -methyltryptamine reported unpleasant feelings with nervous tension, irritability, restlessness, and inability to sleep; 9 out of 12 of these subjects described the effects as being similar to a long-lasting LSD-like drug. Only 2 out of the 11 subjects given α -ethyltryptamine likened its effects to those of LSD.

An interesting comparison between the effects of LSD and those of non-indolic psychotropic drugs was made by Rosenbaum, Cohen, Luby, Gottlieb, and Yelen (1959). They first measured the performance of a group of chronic schizophrenic patients on attention (reaction time), motor function (rotary pursuit), and proprioception (weight discrimination). Similar measurements were then carried out on normal subjects who had received either LSD (1 μ g./kg.), phencyclidine (0.1 mg./kg.), or amobarbital (500 mg.) plus amphetamine sulphate (15 mg.). Phencyclidine was the only drug to produce dysfunction in any way similar to that found in schizophrenics. It was concluded that the drug produced schizophrenia-like impairment of primary attention and motor functions whereas LSD simulated only the secondary symptoms of schizophrenia. This finding is somewhat at variance with that of Beech, Davies, and Morgenstern (1961), who compared the effects of phencyclidine (7.5 mg.) with those of sodium amytal (200 mg.). Neither drug produced scores of thought disorder different from those of non-drugged subjects. The scores from sodium amytal-treated subjects were not significantly different from those from schizophrenic patients with thought disorders. There were significant differences, however, between the scores from phencyclidine-treated subjects and schizophrenic patients.

Hollister, in 1962, gave fixed doses of LSD, mescaline, psilocybin, and a glycolate (JB-329, *see* Chapter 6) to normal subjects and compared the effects with the clinical syndrome of schizophrenia. The first-named three drugs produced a pattern of somatic and perceptual effects without the disorientation, paranoid ideation, disturbed thinking, and auditory, gustatory, olfactory, and tactile hallucinations commonly seen in schizophrenia. JB-329 produced different effects, characteristic of a toxic delirium. Taped interviews with schizophrenic patients and with subjects under the influence of mescaline, psilocybin, and JB-329 were heard by 78 professional raters. In the great majority of cases a correct distinction between drugged and schizophrenic subjects was made. Another glycolic acid ester, JB-336 (*see* Chapter 6) was studied by Balestrieri (1960), who was not able to demonstrate any cross-tolerance between it and LSD. Hollister, Prusmack, Paulsen, and Rosenquist (1960) also reported differences between the clinical effects of some of the glycolic acid esters and those of LSD, mescaline, and psilocybin. Itil and

Fink (1966), working with various types of mental patient, gave either 0.5–2 $\mu\text{g./kg.}$ of LSD or 0.05 mg./kg. of Ditrane. They found differences between the effects of the two types of drug on the E.E.G. pattern.

It is clear from this brief account of a few human studies that the effects of hallucinogenic drugs are manifested in a variety of ways. Objective measurements of certain effects can be made, but basically it is the subjective reaction of the subject that is of the greatest value. Perhaps one of the more valuable contributions of the human experiments has been in cross-tolerance studies from which it has been possible to arrange drugs into groups producing similar effects and presumably acting by similar, if not identical, mechanisms. It has also been possible to compare the effects of drugs with the signs and symptoms of schizophrenia. The general conclusion is that no drug exactly mimicks the naturally-occurring psychoses.

VI. GENERAL CONCLUSIONS

There is, at present, no generally applicable method for detecting hallucinogenic activity except by administering the agent to man and observing its effects. Within specific classes of drug relatively simple pharmacological procedures can be used to give reasonably reliable predictions of activity in man. Thus, among the sympathomimetic amines elevation of rabbit rectal temperature is a satisfactory test procedure, though this does not distinguish adequately between amphetamine-like and LSD-like activities. In order to make this distinction it may be necessary to study the effects of the drugs upon electrocortical activity. Central anti-acetylcholine potency, as measured by blockade of oxotremorine-induced tremors, is likely to be predictive of hallucinogenic activity among the atropine-like drugs. It is, however, a necessary preliminary to ensure that the drugs do indeed possess classical atropine-like activity by using a simple *in vitro* preparation, for example antagonism of acetylcholine-induced contractions of the isolated guinea-pig ileum. There still appears to be no specific test for hallucinogenic activity in cannabinoids, but it is probably safe to say that a compound structurally related to the active naturally-occurring cannabinoids and possessing the same spectrum of pharmacological activity, notably those effects indicative of central nervous system depression, will possess the hallucinogenic activity characteristic of these compounds.

It is clear from these comments that the chances of detecting hallucinogenic activity in a new series of chemical agents is somewhat remote. In most cases such activity will only become apparent

after deliberate or accidental human exposures to the agents. It may then become possible in retrospect to devise adequate animal testing procedures to detect hallucinogenic activity in analogous compounds.

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Chapter 3

Phenylalkylamines and Their Derivatives

I. PHENYLETHYLAMINES

1. NATURAL SUBSTANCES

Mescaline, or 3,4,5-trimethoxyphenylethylamine, has classically been regarded as the paradigm of a hallucinogenic drug. Even as late as 1968 this naturally derived substance, the active constituent of the peyote cactus, occupied the major part of contemporary discussions of hallucinogenic derivatives of phenylethylamine (Hofmann, 1968; Patel, 1968). Mescaline owed its pre-eminent position to its early isolation and identification, and for many years it was the most potent hallucinogen of known chemical structure. Other natural substances, such as psilocybin, were subsequently shown to be more potent than mescaline, which is as far removed in potency from the synthetic lysergic acid diethylamide as aspirin is in analgesic potency from morphine. Furthermore, extensive investigations into phenylethylamines of synthetic rather than natural origin (Shulgin, Sargent, and Naranjo, 1969; Nieforth, 1971) have tended to relegate mescaline from its position of importance, and it can now be regarded as a naturally occurring example with relatively low potency of a much wider group of hallucinogens. Unfortunately, many biochemists and pharmacologists seem to have a mescaline fixation and continue to use this readily available drug for investigations of the mode of action of hallucinogens in general.

Mescaline is only one of a number of hallucinogenic phenylethylamines that have been, and continue to be, found in a variety of plants, particularly North, Central, and South American cacti. The number of species that are called 'peyote' by various Indian tribes, their reputed use as stimulants, narcotics, inebriants, or hallucinogens, and the size of the family *Cactaceae* with over 3000 species,

has prompted a considerable phytochemical search for psychoactive alkaloids (Schultes, 1966, 1970; Brown, Massingill, and Hodgkins, 1968; Agurell, 1969; Agurell, Bruhn, Lundstrom, and Svensson, 1971; Neal, Sato, Howald, and McLaughlin, 1972). It is beyond the scope of this monograph to list them all, particularly since many of them have not been found to be hallucinogenic. Thus, *N*-acetyl-, *N*-methyl-, and *N,N*-dimethylmescaline, together with many of the tetrahydroisoquinolines derived by cyclization of such phenylethylamines, are probably not psychoactive. *N*-Acetyl-3,4-dimethoxyphenylethylamine, for example, though reported to be several-fold more active than the parent amine in behavioural studies in animals, is not hallucinogenic in man even at high doses (Johnson, Friedhoff, Alpert, and Marchitello, 1970). Fig. 3.1 lists the chemical structures of those which are reported to be hallucinogenic. Many of the phenylethylamines found in plants, like dopamine and tyramine,

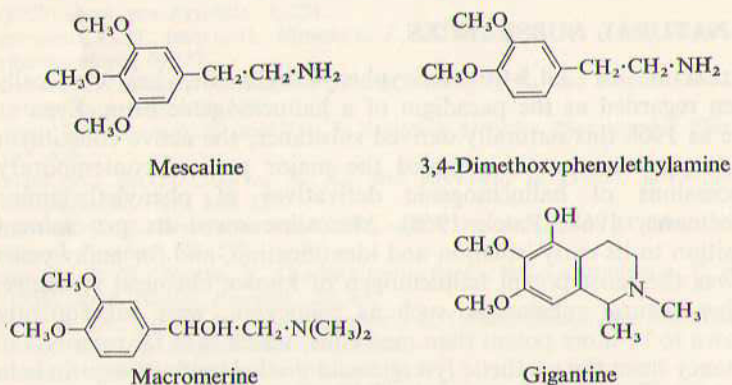


Fig. 3.1.—Naturally occurring hallucinogens derived from phenylethylamine.

merely represent stages in the biosynthesis of mescaline. The existence of an *O*-methyltransferase capable of forming methoxylated phenylethylamines has been demonstrated in the tissues of both plants (Basmadjian and Paul, 1971) and animals (Friedhoff, Schweitzer, and Miller, 1972; Friedhoff, Schweitzer, Miller, and Van Winkle, 1972; Friedhoff, 1973; Hartley and Smith, 1973), and it is likely that much the same biosynthetic processes can take place in either (Fig. 3.2). Whether this possibility of endogenous synthesis of a hallucinogen plays any physiological role *in vivo* in animals or even in man is still very remote, although it recalls the controversy regarding the 'pink spot' when endogenous 3,4-dimethoxyphenylethylamine was implicated in the cause of schizophrenia.

The only hallucinogenic phenylethylamines of natural origin to receive extended attention have been mescaline and 3,4-dimethoxyphenylethylamine (Patel, 1968). Macromerine and gigantine, in initial chemical reports (Hodgkins, Brown, and Massingill, 1967; Brown, McGeer, and Moser, 1968; Kapadia, Rao, Fayez, Chowdury, and Sethi, 1970), were claimed to produce hallucinogenic reactions in

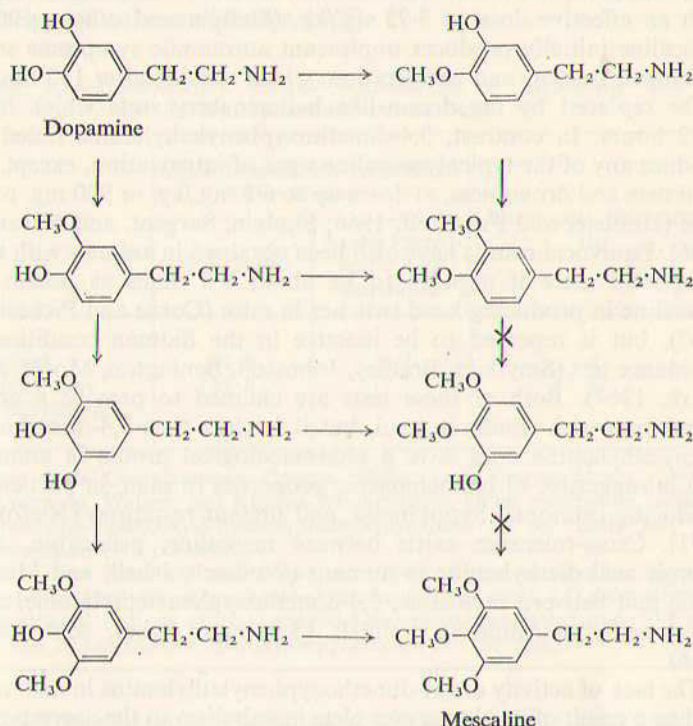


Fig. 3.2—Biosynthesis of mescaline in tissues of plants and animals (adapted from Basmadjian and Paul, 1971; Friedhoff and others, 1972). X Signifies that transformation is yet to be demonstrated.

squirrel monkeys and cats at doses of 20 mg./kg. and 5 mg./kg. (i.p.) respectively; a more recent study has been unable to repeat this finding (Florio, Fuentes, Ziegler, and Longo, 1972) and the compounds have not received trial in man. More recently, macromerine and several derivatives were shown to have no effect on conditioned avoidance responses in rodents despite reaching the brain in concentrations greater than those achieved by a comparable dose of mescaline (Vogel, Evans, Bonnem, Fischer, and McLaughlin, 1973).

Mescaline typically produces in man a syndrome of perceptual distortion, depersonalization, difficulty in thought and expression, rapid flow of thoughts, poor memory, and a dream-like state. It apparently has a rather stronger hallucinatory and a somewhat weaker depersonalizing effect than the more potent lysergic acid diethylamide; on a molar basis the latter is about 5–10,000 times more effective, the usual oral dose of mescaline being 200–600 mg. with an effective dose of 3.75 mg./kg. (Shulgin and others, 1969). Mescaline initially produces unpleasant autonomic symptoms such as nausea, tremor, and perspiration, which subside after 1–2 hours, to be replaced by the dream-like hallucinatory state which lasts 5–12 hours. In contrast, 3,4-dimethoxyphenylethylamine failed to produce any of the typical mescaline signs of intoxication, except for weakness and drowsiness, at doses up to 6.8 mg./kg. or 900 mg. total dose (Hollister and Friedhoff, 1966; Shulgin, Sargent, and Naranjo, 1966). Equivocal results have also been obtained in animals with this compound since it appears to be about 0.6 times as potent as mescaline in producing head twitches in mice (Corne and Pickering, 1967), but is reported to be inactive in the Sidman conditioned avoidance test (Smythies, Bradley, Johnston, Benington, Morin, and Clark, 1967). Both of these tests are claimed to provide a good correlation with results in man, but it is clear that 3,4-dimethoxyphenylethylamine does have a pharmacological profile in animals that is suggestive of hallucinogenic properties in man, in particular producing catatonia, hypokinesia, and pressor responses (Nieforth, 1971). Cross-tolerance exists between mescaline, psilocybin, and lysergic acid diethylamide in humans (Wolbach, Isbell, and Miner, 1962) and between mescaline, 3,4-dimethoxyphenylethylamine, and *N,N*-dimethylmescaline in animals (Smythies, Sykes, and Lard, 1966).

The lack of activity of 3,4-dimethoxyphenylethylamine in man may well be a result of its almost complete metabolism to the corresponding acid, in contrast to the significant amounts of mescaline excreted as free base (*Table 3.1*). Oxidative deamination of the two compounds appears to be little different in rabbit liver (Clark, Benington, and Morin, 1965), but only that of mescaline is significantly blocked by semicarbazide, indicating alternative metabolic routes for 3,4-dimethoxyphenylethylamine. However, oxidative deamination of the latter in rodent brain mitochondria occurs at a rate four times that of mescaline, although the two compounds are accumulated into brain tissue at much the same rate (Shah and Himwich, 1971). This rate difference is reflected in the respective half-lives of the drugs and in the amounts of free base excreted unchanged in the urine (*Table 3.1*). Similar results are apparent in animals, and both

compounds are rapidly absorbed from the intestinal tract to be concentrated in the kidney, liver, spleen, and heart (Neff, Rossi, Chase, and Rabinowitz, 1964; Vogel, 1968). Relatively low concentrations are achieved in the brain, figures of less than 0.14 per cent of intravenously administered mescaline being quoted for rats (Denber and Teller, 1970), but mescaline appears to concentrate in synaptic regions of the brain in contrast to 3,4-dimethoxyphenylethylamine (Denber and Teller, 1968).

Table 3.1.—COMPARATIVE HUMAN METABOLISM OF Mescaline AND 3,4-DIMETHOXYPHENYLETHYLAMINE

	MEAN PERCENTAGE RECOVERED /24 hr. URINE		BIOLOGICAL HALF-LIFE (h)
	Free Base	As the Phenyl- acetic Acid Derivative	
Mescaline*	81.9	26.2	6
3,4-Dimethoxy- phenylethylamine†	15.5	77	<1.0

*Data from Charalampous, Orengo, Walker, and Kinross-Wright (1964); Charalampous, Walker, and Kinross-Wright (1966). Other metabolites include N-acetyl-2-(3,4-dimethoxy-5-hydroxyphenyl)ethylamine (5 per cent) and N-acetylmescaline (<1 per cent).

†Data from Friedhoff and Schweitzer (1968). Other metabolites include N-acetyl-3-methoxy-4-hydroxyphenylethylamine (6.2 per cent), 2-(3,4-dimethoxyphenyl)ethanol (0.1 per cent), N-acetyl-3,4-dimethoxyphenylethylamine (0.1 per cent), and 2-(3-methoxy-4-hydroxyphenyl)ethanol (0.1 per cent).

3,4,5-Trimethoxyphenylacetic acid seems to be the major metabolite of mescaline in man, and while other urine metabolites have been detected (Hofmann, 1968; Patel, 1968) it is likely that it is the sole brain metabolite of the drug. 3,4-Dimethoxyphenylethylamine, on the other hand, is metabolized by routes other than oxidative deamination (Table 3.1). The period of maximum behavioural changes elicited in humans by mescaline occurs 1–2 hours after the period of maximal blood levels and excretion of the drug has been reached, which has aroused speculation that it is a metabolite of mescaline which produces the hallucinogenic effects (Stevenson and Makrach, 1959). 3,4,5-Trimethoxyphenylacetic acid, however, produces no behavioural changes in animals and is not hallucinogenic when given orally to humans (Charalampous and others, 1964).

Nevertheless, administration of 2-(3,4,5-trimethoxyphenyl)ethanol or 3,4,5-trimethoxyphenylacetaldehyde, neither of which has been positively identified as a brain metabolite of mescaline in man, together with appropriate inhibitors of their enzymic degradation, produced behavioural effects in rats at doses lower than those required for mescaline itself (Goldstein, Friedhoff, Pomerantz, Simmons, and Contrera, 1961; Friedhoff and Goldstein, 1962). These effects have not been confirmed, and extensive investigations of the pharmacology of a series of phenylethanols, phenylpropanols, phenylpropanones, and phenylpropenes, which represent possible metabolites of hallucinogenic phenylethylamines or amphetamines, revealed only a slight depressant action on the central nervous system of rodents (Barfknecht, Miles, and Leseney, 1970; Barfknecht, Smith, Nichols, Leseney, Long, and Engelbrecht, 1971; Engelbrecht, Long, Nichols, and Barfknecht, 1972).

Certainly, the effects of mescaline on conditioned avoidance responses in rats are enhanced by pretreatment with iproniazid, suggesting that the free amine and not a metabolite is responsible (Smythies, Johnston, and Bradley, 1967). Furthermore, a re-evaluation of the information concerning the time-courses of the metabolism of mescaline, its presence in the brain, and its central effects, has concluded that the latter two parameters do indeed correspond (Charalampous and others, 1966). It is significant, however, that on raphe neurons, a possible site of action for hallucinogens, mescaline has different effects when administered systematically or microiontophoretically in contrast to the identical effects of LSD (Haigler and Aghajanian, 1973).

2. STRUCTURE-ACTIVITY RELATIONSHIPS

Mescaline is by no means the most potent hallucinogenic phenylethylamine (Table 3.2). Early studies (Benington, Morin, and Clark, 1960) showed that 3,4,5-trimethyl-, 4-methyl-, 4-chloro-, 3,5-dimethyl-4-methoxy-, 3,4-dichloro-, 3,4-dimethyl-, and 3,5-dimethoxy-4-methyl-phenylethylamine, all produced the sham rage response in cats, a syndrome that has been equated with hallucinogenic activity in man. Structure-activity studies using a rope-climbing test in rats demonstrated that removal of the 5-methoxyl group from mescaline halved its potency, demethylation of the 4-methoxy caused complete loss of activity, but replacement by a 4-benzyloxy increased activity (Smythies and Levy, 1960). The most comprehensive and reliable study in animals is by Smythies, Bradley, and their colleagues (1967) using several conditioned avoidance profiles. Of all the possible methoxylated phenylethylamines, only two compounds

exceeded mescaline in its disruption of behaviour; 2,3,4,5-tetramethoxy- and 2,3,4,5,6-pentamethoxy-phenylethylamines were respectively twice and eight times as potent as the parent alkaloid, but neither seems to have been tested in man. More recently (Ho, Tansey, Balster, An, McIsaac, and Harris, 1970), 2,5-dimethoxy-4-methylphenylethylamine has been found to be about five times as potent as mescaline in disrupting animal conditioned avoidance responses although Beaton, Smythies, Benington, and Morin (1969) report it to be less than 2.5 times as potent unless it is given concomitantly with an inhibitor of monoamine oxidase. 4-Methoxyphenylethylamine, which was ineffective in this respect (Smythies, Bradley, and others, 1967), produced a mescaline-like syndrome in cats of powerful central and sympathomimetic stimulation (Walker, Willis, and Willis, 1970), but the compound is not hallucinogenic in man (Brown, McGeer, and Moser, 1968).

Several phenylethylamines have been tested in man by Shulgin's group (Shulgin and others, 1969), who found the most effective compound, 2-methoxy-3,4-methylenedioxyphenylethylamine, to be

Table 3.2.—RELATIVE HALLUCINOGENIC POTENCIES OF SOME PHENYLETHYLAMINES

R	Disruption of Conditioned Avoidance Response (rats)*	Hallucinogenic Effective Dose (man)†
3,4,5-(OCH ₃) ₃ ‡	1.0	1.0
2,3,4,5-(OCH ₃) ₄	2	NT
2,3,4,5,6-(OCH ₃) ₅	8	NT
4-CH ₃ -2,5-(OCH ₃) ₂	<2.5,5§	NT
4-OCH ₃	<1	<1
3,4-(OCH ₃) ₂	<1	0.2
2,4,5-(OCH ₃) ₃	<1	1
2-OCH ₃ -3,4-OCH ₂ O	NT	<5
3-OCH ₃ -4,5-OCH ₂ O	NT	1

* ED₁₀₀ for mescaline in disrupting the Sidman Avoidance Schedule and producing a Bovet-Gatti profile is 25 mg/kg. (i.p.) (Smythies, Bradley, and others, 1967; Beaton and others, 1969).

† The orally effective dose of mescaline (the mean of the threshold and maximally effective doses), which is accurate to ± 25 per cent, is 3.75 mg/kg. (Shulgin and others, 1969).

‡ Mescaline.

§ ED₅₀ for mescaline in disrupting conditioned operant behaviour is 38 μ moles/kg. (Ho, Tansey, and others, 1970).

N.T., Signifies not tested.

about five times as potent as mescaline (*Table 3.2*). The hallucinogenic effects in man of 2,4,5-trimethoxyphenylethylamine are the source of some dispute, and it is claimed to be both equal to mescaline (Shulgin and others, 1969) and totally inactive (Dittrich, 1971). It is interesting that the latter study suggested that pretreatment with this compound actually potentiated the hallucinogenic effects of subsequent doses of mescaline, an observation in contrast to the animal studies where such pretreatment antagonized the effects of mescaline (Smythies, Johnston, and Bradley, 1967). There seems little correlation between the susceptibility to oxidative deamination of phenylethylamines and their hallucinogenic potency, although it is significant that 2,3,4,5,6-pentamethoxy- and 2,3,4,5-tetramethoxy-phenylethylamines are not affected by monoamine oxidase from rabbit liver (Clark and others, 1965). However, it is likely that the central metabolism of phenylethylamines differs in man from that in animals, while even in the latter it is clear that compounds such as 2,6-dimethoxy- or 2,3,6-trimethoxy-phenylethylamine, which are relatively unaffected by monoamine oxidase, are without behavioural effects. In view of the difficulties in interpretation which differing rates of enzymic degradation present for structure-activity relationships, it seems more pertinent to use the α -methylphenylethylamines (the amphetamines), which are not only more potent (Shulgin and others, 1969) but also more resistant to the actions of amine oxidases (Hellot, Lauquin, and Pacheco, 1970).

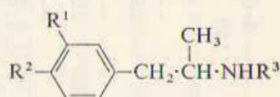
II. OTHER PHENYLALKYLAMINES

More is known of structure-activity relationships among derivatives of phenylethylamine than any other group of hallucinogenic drugs, chiefly because they are readily available by synthetic manipulation of all parts of the molecule (Shulgin, 1973a). This is in contrast to the tryptamines or tetrahydrocannabinols, which are relatively difficult to synthesize, and lysergic acid diethylamide, whose structure is not readily amenable to extensive synthetic variation. Of all the possible structural changes that have been rung on the phenylethylamine molecule, the one which confers the maximal hallucinogenic potency is α -methylation to give the amphetamines or phenylisopropylamines.

1. AMPHETAMINES

Amphetamine itself (**3.1**) has a wide pharmacological spectrum which is susceptible to dramatic alteration by subtle changes in the molecule (Costa and Garattini, 1970), ranging from the prominent

anorectic properties of N-ethyl-3-trifluoromethylamphetamine (fenfluramine, 3.2) to the equally prominent locomotor stimulation provided by 3-bromo-4-methoxyamphetamine (3.3) (Barfknecht and Nichols, 1971). It is interesting that amphetamines like fenfluramine, of relatively poor potency as central stimulants, block many of the actions in animals of the more potent amphetamines in this respect, suggesting a possible clinical application in the prophylactic treatment of amphetamine abuse (Berger, 1972). Amphetamine is not hallucinogenic in single doses, although chronic administration may result in a toxic psychosis indistinguishable from paranoid



(3.1) $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$

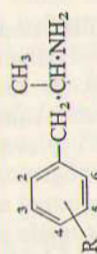
(3.2) $\text{R}^1 = \text{CF}_3$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{C}_2\text{H}_5$

(3.3) $\text{R}^1 = \text{Br}$; $\text{R}^2 = \text{OCH}_3$; $\text{R}^3 = \text{H}$

schizophrenia with attendant hallucinations (Ellinwood, 1967, 1968; Griffith, Cavanagh, and Oates, 1970). Hallucinogenic amphetamines in the classical sense, which produce a mescaline-like syndrome in a single dose, are obtained by suitable substitution of the aryl moiety of amphetamine (Tables 3.3–3.5). Nevertheless, such compounds often possess a mixture of hallucinogenic, central stimulant, and other properties. In this monograph quoted activities are those for hallucinogenic effects and no attempt is made to define structure–activity relationships for other types of biological activity, which may well be expected to be different.

The presence of trimethoxy substitution in mescaline undoubtedly prompted many of the studies of the effects upon hallucinogenic potency of the position and number of methoxy groups in the aryl nucleus of amphetamines (Table 3.3). Results in a variety of animal species and behavioural tests generally parallel those obtained in man; thus, disruption of conditioned avoidance responses (Smythies, Johnston, Bradley, Benington, Morin, and Clark, 1967; Smythies, Johnston, and Bradley, 1969) or of the swimming abilities (Uyeno, 1968, 1971; Ho, McIsaac, An, Tansey, Walker, Englert, and Noel, 1970) of rodents together with impairment of discriminatory abilities in monkeys (Uyeno, Otis, and Mitoma, 1968; Uyeno, 1969) and the production of hyperthermia in rabbits (Aldous, Barrass, Brewster, Buxton, Green, Pinder, Rich, Skeels, and Tutt, 1974) agree with the clinical observations (Shulgin and others, 1969) that high potency is favoured by 2,4,5-trisubstitution. In general, it is clear from Table 3.3. that 2,4,5-trimethoxyamphetamine (3.14) is by far the most potent

Table 3.3.—STRUCTURE-ACTIVITY RELATIONSHIPS IN METHOXYAMPHETAMINES. RELATIVE POTENCIES IN BEHAVIOURAL TESTS*



Compound No.	R	Man†	Mouse‡	Rat 1§	Rat 2	Squirrel¶ Monkey	Rabbit**
	MESCALINE	1.0	1.0	1.0	—	1.0	0.02
	LSD	4000	—	—	1000	550	1000
3.4	4-OCH ₃	5	—	8	—	—	—
3.5	2,3-(OCH ₃) ₂	—	0.5	0	—	—	—
3.6	2,4-(OCH ₃) ₂	5	—	—	—	—	—
3.7	2,5-(OCH ₃) ₂	8	1.0	0	—	—	0.9††
3.8	3,4-(OCH ₃) ₂	<1	1.0	2	—	—	—
3.9	3,5-(OCH ₃) ₂	—	2.5	0	—	—	—
3.10	3,4,5-(OCH ₃) ₃	2.2	1.5	2	61	1.8	1.1††
3.11	2,3,4-(OCH ₃) ₃	<2	—	<1	25	0.65	—
3.12	2,3,5-(OCH ₃) ₃	4	—	—	—	1.1	—
3.13	2,3,6-(OCH ₃) ₃	13	—	—	—	—	—
3.14	2,4,5-(OCH ₃) ₃	17	0.3	<2	126	5.5	3.3
3.15	2,4,6-(OCH ₃) ₃	10	—	1.2	—	3.2	—
3.16	2,3,4,5-(OCH ₃) ₄	6	—	—	—	—	—

* —, Not available; 0, Inactive.

† The effective oral dose of mescaline (mean of threshold and maximally effective doses) is 3.75 mg./kg., accurate to ± 25 per cent (Shulgin and others, 1969).

‡ Disruption of ability of mice to negotiate a T-shaped swim maze 30 minutes after injection (i.p.) expressed as a summation of increased time and errors. Mescaline is effective at 50 μ moles/kg. (Ho, McIsaac, and others, 1970).

§ Disruption of conditioned avoidance response behaviour, based upon the Sidman Avoidance Schedule and Bovet-Gatti profiles; the ED_{100} of mescaline (i.p.) is 25 mg./kg. (Smythies, Johnston, and others, 1967).

|| Production of starting latency in rats trained to swim under water. The ED_{50} of LSD is 1.9 μ moles/kg. which is the dose required to produce a latency of greater than 1.6 seconds in half of the treated animals (Uyeno, 1968, 1971). Results obtained in a similar swim-maze test are identical (Uyeno and Mitoma, 1969).

¶ Disruption of the ability of animals trained to discriminate between two black disks of different sizes. The ED_{50} of mescaline (i.p.) is 82.2 μ moles/kg. (Uyeno, 1969; Uyeno and others, 1968).

** Production of hyperthermia in rabbits as measured by rectal temperature. A dose of 0.006 μ mole/kg. (i.v.) of LSD produces a rise of 1°C. (Aldous and others, 1974).

†† Though producing hyperthermia in rabbits, these compounds are amphetamine-like rather than LSD-like in their effects on cat E.E.G. or open-field behaviour in rodents.



methoxylated derivative of amphetamine, being 17 times as active as mescaline in man. The importance of the α -methyl group is demonstrated by the higher potency of 3,4,5-trimethoxyamphetamine (3.10) over that of mescaline, the former compound having been one of the first amphetamines to provoke interest in their hallucinogenic properties (Peretz, Smythies, and Gibson, 1955; Shulgin, Bunnell, and Sargent, 1961). The higher activity reported for 4-methoxyamphetamine (3.4) in rats trained on the Sidman Avoidance Schedule (Smythies, Johnston, and others, 1967) is not reproduced in man, although its potency ratio to mescaline is much the same. Smythies has suggested that amphetamine-induced psychosis is a result of human metabolism to this compound, but the latter could

Table 3.4.—STRUCTURE—ACTIVITY RELATIONSHIPS IN ALKOXY-AMPHETAMINES. RELATIVE POTENCIES IN BEHAVIOURAL TESTS*

Compound No.	R	Man	Mouse
	MESCALINE	1.0	1.0
3.17	3,4-OCH ₂ O	3	3.5
3.18	3-OCH ₃ -4,5-OCH ₂ O	2.7	—
3.19	2-OCH ₃ -4,5-OCH ₂ O	12	—
3.20	2-OCH ₃ -3,4-OCH ₂ O	10	—
3.21	2,3-OCH ₂ O-4-OCH ₃	3	—
3.22	2,5-(OCH ₃) ₂ -3,4-OCH ₂ O	12	—
3.23	2,3-(OCH ₃) ₂ -4,5-OCH ₂ O	5	—
3.24	3-OCH ₃ -4,5-O(CH ₂) ₂ O	<1	—
3.25	2-OC ₂ H ₅ -4,5-(OCH ₃) ₂	<7	—
3.26	2,5-(OCH ₃) ₂ -4-OC ₂ H ₅	15	—
3.27	2,4-(OCH ₃) ₂ -5-OC ₂ H ₅	<7	—

*For an explanation of the tests, see Table 3.3.

not be detected in humans fed large oral doses of amphetamine (Angrist, Schweitzer, Friedhoff, and Gershon, 1970). Furthermore, 2,5-dimethoxyamphetamine (3.7) is more potent than either the 3,4-(3.8) or 2,4-analogues (3.6), and the presence of a 4-methoxyl is clearly not a prerequisite for high activity in this series. Nevertheless, 4-methoxyamphetamine resembles other hallucinogenic amphetamines in blocking conditioned discrimination behaviour in cats and in causing bizarre behavioural patterns which have been interpreted as hallucinatory (Florio and others, 1972). The compound did not concomitantly produce the clear-cut activation of the E.E.G. seen with highly active amphetamines like DOM

(3.28, Table 3.5) but it elicited the typical behavioural syndrome in doses lower than those required of 3,4,5-trimethoxyamphetamine.

There are few reports of the effect upon potency of alkoxy substituents other than methoxy (Table 3.4). Shulgin (1968) has described the preparation of most of the ethoxy analogues of the active methoxyamphetamines, but only three of these have undergone pharmacological evaluation. Replacement of the 4-methoxy substituent of 2,4,5-trimethoxyamphetamine by ethoxy is apparently less deleterious than replacement of the 2- or 3-methoxy groups; thus, 3.26 has a potency of 15 compared to the parent compound's 17 in man, whereas the isomeric forms (3.25) and (3.27) are less than half as effective (Shulgin and others, 1969). In contrast, the methylenedioxyamphetamines have been thoroughly investigated as a consequence of their possible formation *in vivo* from constituents of many natural oils, such as safrole and myristicin; the hallucinogenic activity of nutmeg, which contains these compounds, has now been shown to be due not to their transformation to amphetamines but possibly to other nitrogenous metabolites (see Chapter 7). Shulgin's initial report showed that 3-methoxy-4,5-methylenedioxyamphetamine (3.18) produced a mescaline-like syndrome in man, but at doses 2-3 times less than that required of the natural hallucinogen (Shulgin, 1964a), and this result has been confirmed in cats, rats, and rabbits (Florino and others, 1972). The ethylenedioxy and trimethylenedioxy analogues, which contain larger rings in the 4,5-positions, appear to have no hallucinogenic activity in man or rodents (Shulgin, 1964a).

A more extensive study (Shulgin, 1964b) confirmed these findings and suggested that the activities of 2-methoxy-4,5-methylenedioxyamphetamine (3.19) and 2-methoxy-3,4-methylenedioxyamphetamine (3.20) were as high as 21 and 18 times that of mescaline, although these figures have been revised to 12 and 10 respectively (Shulgin and others, 1969). Activity is somewhat reduced when the methylenedioxy group is in other positions, 2,3-methylenedioxy-4-methoxyamphetamine (3.21) being only three times as potent as mescaline, and the importance of the 2-methoxy group in the series is again emphasized by the low equipotency of 3,4-methylenedioxyamphetamine (3.17) and 3-methoxy-4,5-methylenedioxyamphetamine (3.18) compared to the high potency of compounds containing this substituent (3.19, 3.20) (Table 3.4). Most of these compounds produce a typical mescaline syndrome, particularly of closed-eye imagery (Shulgin, Sargent, and Naranjo, 1973), in contrast to that produced by tetrasubstituted derivatives such as 2,5-dimethoxy-3,4-methylenedioxyamphetamine (3.22) and 2,3-dimethoxy-4,5-methylenedioxyamphetamine (3.23) (Shulgin and Sargent, 1967).

These latter two compounds are considered to be different from the true hallucinogenic amphetamines, producing mild perceptual distortion, increased emotional affect and empathy, together with euphoria and lack of anxiety. They also differ from compounds like mescaline and the trimethoxyamphetamines in not producing autonomic distress prior to the onset of intoxication, although mild

Table 3.5.—STRUCTURE-ACTIVITY RELATIONSHIPS IN ALKYL- AND HALO-AMPHETAMINES. RELATIVE POTENCIES*

Compound No.	R	Man	Mouse	Rat 1	Squirrel		Rabbit
					Rat 2	monkey	
MESCALINE		1.0	1.0	1.0	—	1.0	0.02
LSD		4000	—	—	1000	550	1000
3.28	2,5-(OCH ₃) ₂ -4-CH ₃	80	3.5	5.0, 7.0†	200	28	30
3.29	2,5-(OCH ₃) ₂ -4-C ₂ H ₅	150	—	—	405	63	69
3.30	2,5-(OCH ₃) ₂ -4-(<i>n</i> -C ₃ H ₇)	—	—	—	—	—	72
3.31	2,5-(OCH ₃) ₂ -4-(<i>iso</i> -C ₃ H ₇)	—	—	—	—	—	4.9
3.32	2,5-(OCH ₃) ₂ -4-(<i>t</i> -butyl)	—	—	—	—	—	4.3
3.33	2,5-(OCH ₃) ₂ -4-Br	> 150	—	> 10	—	—	123
3.34	2,5-(OCH ₃) ₂ -4-Cl	—	—	—	—	—	114
3.35	2-OCH ₃ -4-CH ₃	—	0.3	—	—	—	2.4
3.36	3-OCH ₃ -4-CH ₃	—	5.5	—	—	—	—
3.37	2-OCH ₃ -4-Cl	—	—	—	—	—	5.0
3.38	3-OCH ₃ -4-Cl	—	—	—	—	—	0.9
3.39	3-OCH ₃ -4-Br	—	—	3.3	—	—	—
3.40	2-Br-5-OCH ₃	—	—	0	—	—	—
3.3	3-Br-4-OCH ₃	—	—	2.8	—	—	—
3.41	3,5-(OCH ₃) ₂ -4-Br	—	—	> 2.5	—	—	—
3.42	2-Br-4,5-(OCH ₃) ₂	—	—	0	—	—	—
3.43	4-CH ₃	—	—	0	—	—	< 0.3‡
3.44	4-Br	—	—	—	—	—	< 0.3‡
3.45	4-Cl	—	—	0	—	—	< 0.3‡
3.46	2,4-Cl ₂	—	—	—	—	—	1.0‡
3.47	2,4,5-Cl ₃	—	—	—	—	—	0.2‡

*For an explanation of these tests, see Table 3.3.

†Disruption of a conditioned operant response, the ED₅₀ of mescaline being 38 µmoles/kg. (i.p.) (Ho, Tansey, and others, 1970).

‡Not a true mescaline-like (or LSD-like) effect, since typical hallucinogenic profiles are not obtained in the cat E.E.G. or in open field behaviour in rodents.

incoordination has been noted in man. 3,4-Methylenedioxy-amphetamine also seems atypical and has been suggested as a useful adjunct to psychotherapy (Naranjo, Shulgin, and Sargent, 1967); it enhances intellectual and emotional thinking, together with an increase in the level of fluency and attention, at dose levels less than those required for the appearance of imagery and perceptual distortion (Thiessen and Cook, 1973).

The most potent hallucinogenic members of the amphetamine series are those which contain other substituents, particularly in the 4-position, in addition to methoxy (*Table 3.5*). Nevertheless, compounds which do not contain methoxy groups are not psychotomimetic although they may be amphetamine-like in producing locomotor stimulation; 4-bromo (**3.44**), 4-chloro- (**3.45**), 4-fluoro-, 4-methyl (**3.43**), 3,4,5-trimethyl, 2,4-dichloro (**3.46**), and 2,4,5-trichloro-amphetamine (**3.47**) do not produce the full hallucinogenic syndrome in most animal species (Beaton, Smythies, Benington, Morin, and Clark, 1968; Smythies and others, 1969; Aldous and others, 1974). The highly active, 2,5-dimethoxy-4-methylamphetamine (DOM, STP, **3.28**) was first identified in an illicit sample of drug, and was claimed by its users to produce effects lasting greater than 72 hours with potentiation by the usual hallucinogen antagonists like chlorpromazine. Subsequent scientific evaluations (Snyder, Faillace, and Hollister, 1967; Hollister, MacNicol, and Gillespie, 1969) showed these claims to be false, the effects of DOM lasting less than 24 hours and being attenuated by chlorpromazine. The drug is a potent hallucinogen, however, doses of 3–5 mg. producing mental changes with marked hallucinations 1 hour after oral administration, peaking after 3–5 hours, and lasting for 7–8 hours. Only mild euphoria was noted the next day and in only a small proportion of subjects. The typical hallucinogenic triad of symptomatology was evident: physiological effects like nausea, sweating, paraesthesia, tremors, and increased systolic blood-pressure; sensory changes such as blurred vision, multiple imagery, vibration of objects, distorted shapes, visual hallucinations, enhancement of detail, slowed passage of time, and increased contrasts; and psychic phenomena like loss of thought control, elation, difficulty in expression of self, floods of thought, blankness of mind, and ease of distraction. The autonomic effects are undoubtedly due to the strong pressor action of DOM (Huang and Ho, 1972), a feature common to many of the classical hallucinogens. DOM shows tachyphylaxis in that a second dose given to animals 24 hours later does not produce hallucinogenic behaviour, and antagonists include methysergide, 2-bromolysergic acid diethylamide, and chlorpromazine, but not reserpine, α -methyl-tyrosine, *p*-chlorophenylalanine, phenoxybenzamine, propranolol,

atropine, or diphenhydramine (Wallach, Friedman, and Gershon, 1972; Horita and Hill, 1973). Its actions on the E.E.G. are similar to those induced by LSD and mescaline (Florio and others, 1972; Wallach and others, 1972; Aldous and others, 1974), and it clearly acts in a similar way in the central nervous system.

Low doses of DOM produce only a mild euphoria and increased self-awareness in man, with no hallucinogenic effects, and this dose-related dichotomy has also been observed with the analogous compounds, 2,5-dimethoxy-4-ethylamphetamine (DOET, 3.29) (Snyder, Faillace, and Weingartner, 1968, 1969) and 2,5-dimethoxy-4-bromoamphetamine (3.33) (Shulgin, Sargent, and Naranjo, 1971). These milder effects are apparent at dose levels at which DOM produces hallucinogenic symptoms, and it is likely that the latter two compounds represent the most potent hallucinogenic amphetamines so far discovered, though it must be emphasized that the minimum perceptible dose is much closer to the hallucinogenic dose for DOM than it is for DOET or 3.33. Their activity, and that of DOM, has been confirmed in behavioural studies in mice (Ho, McIsaac, and others, 1970; Kulkarni, 1973), rats (Beaton, and others, 1968; Beaton and others, 1969; Smythies and others, 1969; Ho, Tansey, and others, 1970; Barfknecht and Nichols, 1971; Uyeno, 1971; Florio and others, 1972), squirrel monkeys (Uyeno, 1969), and rabbits and cats (Florio and others, 1972; Aldous and others, 1974).

The *N*-propyl homologue of DOM (3.30) is even more potent than DOET in producing hyperthermia in the rabbit with true hallucinogenic profiles in open-field tests in rats and E.E.G. responses in cats, but branched alkyl groups such as *isopropyl* or *tert.*-butyl have a profound deleterious effect (Table 3.5). Neither these compounds nor 2,5-dimethoxy-4-chloroamphetamine, which seems to be as potent as the 4-bromo analogue in animals, have yet been tested in man.

Structure-activity relationships in the series demonstrate the necessity of all three substituents, since analogues of DOM, 4-bromo-2,5-dimethoxyamphetamine, or 4-chloro-2,5-dimethoxyamphetamine, which contain only two of these (3.3, 3.35-3.40) are relatively ineffective in animals. Recent reports (Sepulveda, Valenzuela, and Cassels, 1972) indicate that 2-bromo-4,5-methylenedioxy- and 5-bromo-2,4-dimethoxy-amphetamines are respectively 1.2 and 4.4 times more potent than mescaline in man. Similar deleterious effects are apparent when the positions of the three substituents are interchanged (3.41 and 3.42). The influence of replacement of the methoxyls at positions 2 and 5 by halogen has not been studied, although several of the requisite compounds are

available (Hellot, Violland-Duperret, and Pacheco, 1970). It is interesting that the amino-acid analogue of DOM, 2,5-dimethoxy-4, α -dimethylphenylalanine, is not decarboxylated by rodents *in vivo*, and the compound probably does not have hallucinogenic potential as a precursor to the amphetamine (Ho, Tansey, and Huang, 1971) (Fig. 3.3).

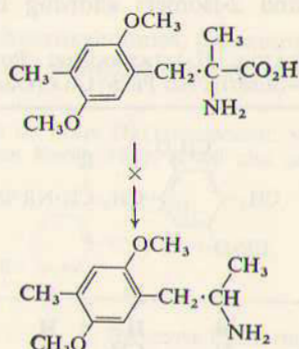


Fig. 3.3.—2,5-Dimethoxy-4-methylamphetamine (DOM, STP) is not formed *in vivo* by decarboxylation of the amino-acid, which is not a substrate for rodent decarboxylases.

2. N-SUBSTITUTED PHENYLALKYLAMINES

A variety of structural changes have been made to the terminal amino group of phenylethylamines and amphetamines, and have generally resulted in greater specificity of action with regard to such properties as central stimulation and anorexia (Biel, 1970). The situation with hallucinogenic phenylalkylamines is less clear.

N-methylation or N-ethylation of DOM (3.28) and the corresponding phenylethylamine (3.48) resulted in compounds (3.49–3.52) which were less potent than the parent drugs in disrupting conditioned operant responses in rats (Ho, Tansey, and others, 1970), and in producing hyperthermia in rabbits, hallucinogenic E.E.G. profiles in cats, and behavioural changes in rats in the open-field situation (Aldous and others, 1974) (Table 3.6). The compounds tended to be amphetamine-like with almost total loss of hallucinogenic activity. This is in contrast to the results of Knoll's group in Budapest, who have generally found that N-methylation enhances the activity, particularly of mono-substituted amphetamines (Table 3.7) (Knoll, Vizi, and Ecséri, 1966; Knoll, 1970). Relationships between structure and activity, which in these studies was measured by the production of sham-rage responses in cats and of latency in the time required for

rats to perform unconditioned escape responses, demonstrated the necessity of proper substitution in the 4-position. Many of these compounds showed LSD-like activity of a high order in these tests, which was confirmed by the production of low-amplitude, fast-activity E.E.G. profiles in rats and rabbits; this 'flattening' effect was evident only with the 4-substituted derivatives, the non-hallucinogenic 3- and 2-isomers showing the desynchronization

Table 3.6.—RELATIVE HALLUCINOGENIC POTENCIES OF SOME N-SUBSTITUTED PHENYLALKYLAMINES

$$\text{CH}_3\text{O}-\text{C}_6\text{H}_2(\text{CH}_3)(\text{CH}_3\text{O})-\text{CH}_2-\text{CH}(\text{R}^1)-\text{NR}^2\text{R}^3$$

Compound No.	R ¹	R ²	R ³	Rat*	Rabbit†
3.48	H	H	H	0.75	—
3.49	H	CH ₃	H	0.10	—
3.50	H	CH ₃	CH ₃	0.12	—
3.28	CH ₃	H	H	1.0	1.0
3.51	CH ₃	CH ₃	H	0.25	0.036‡
3.52	CH ₃	C ₂ H ₅	H	—	0.027‡

*Disruption of conditioned operant responses, the ED₅₀ of 3.28 being 5.4 μmoles/kg. (i.p.) (Ho, Tansey, and others, 1970).

†Production of hyperthermia in rabbits, the dose required of 3.28 to produce a 1°C rise in rectal temperature being 0.2 μmole/kg. (i.v.).

‡These compounds produce amphetamine-like profiles in the cat E.E.G. and open-field behaviour in rodents.

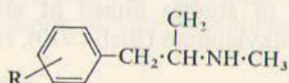
typical of N-methylamphetamine. The latter compounds also resembled N-methylamphetamine in producing hypermotility, in contrast to their hallucinogenic 4-substituted analogues. 4-Bromo-N-methylamphetamine was chosen for further study because of its favourable therapeutic index, although the 4-chloro and 4-nitro compounds are slightly more potent (Table 3.7). The drug is about one-tenth as potent as LSD in a variety of behavioural tests (Knoll, Vizi, and Knoll, 1970).

The apparently high potencies of the N-methylamphetamines compared to those of LSD and mescaline, and the conflicting reports of the effects of N-alkylation upon the activity of DOM, suggest that Knoll's compounds should be studied in other behavioural situations. They resemble LSD and mescaline in rapidly producing tolerance in animals, with a resulting cross-tolerance between the three types of drug (Knoll and Vizi, 1970; Knoll, Vizi, and Knoll,

1970, 1971). It is interesting that the 3-substituted compounds are hydroxylated at the 4-position *in vivo* as might be expected for an amphetamine derivative, a process which enhances hallucinogenic activity. Thus, 3-bromo-4-hydroxy-N-methylamphetamine produces a typical LSD-like behavioural profile in animals, though the parent 3-bromo-N-methylamphetamine is virtually without effect (Knoll and others, 1971).

A number of aralkylhydroxylamines, for example 3.53, have been reported to possess central stimulant properties in animals, although

Table 3.7.—ACTIVITIES OF SOME HALLUCINOGENIC N-METHYLAMPHETAMINES (data from Knoll, 1970; Knoll and others, 1966)



R	LD ₅₀ (s.c., rats, mg./kg.)	EFFECTIVE DOSES (mg./kg., s.c.)	
		Rage (cats)*	Unconditioned Response (rats)†
H	—	0	6.0
4-Cl	55	12.5	7.2
4-Br	320	15	10.0
4-I	265	45	25.0
4-NO ₂	68	15	7.0
4-NH ₂	280	20	37.0
4-OH	330	40	53.0
3-Cl	> 400	30	18.0
3-Br	310	30	16.0
3-NO ₂	90	15	13.5
2-Cl	185	0	—
2-Br	200	0	0
2-NO ₂	280	0	0
LSD	—	1.2	1.1
Mescaline	—	180	200

*Production of a hallucinogenic syndrome in cats (essentially a sham-rage response). Doses quoted are ED₁₀₀ values.

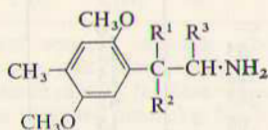
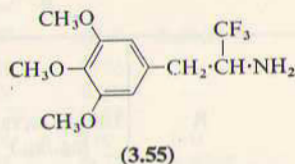
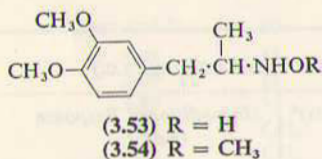
†Production of latency in the time required for rats to jump to the rim of a glass cylinder when placed on a metal plate at the bottom heated to 45°C. (unconditioned escape behaviour). Doses quoted are ED₉₅ values.

0, Signifies ineffective at half the LD₅₀ dose. Only the 4-substituted compounds produce LSD-like E.E.G. profiles in rats and rabbits, while they do not produce locomotor stimulation.

the corresponding methyl ethers (3.54) appear to be central depressants (Benington, Morin, and Clark, 1965). Several of the compounds produced hyperthermia and sham-rage responses in cats, and in view of their possible metabolism to the corresponding amphetamines it would be of interest to see the effects of hydroxyl-amino derivatives of such compounds as DOM and DOET. Certainly, such derivatives of hallucinogenic indolealkylamines like α -methyltryptamine had pharmacological profiles closely similar to those of the parent compounds (Lessin, Long, and Parkes, 1966).

3. MISCELLANEOUS PHENYLALKYLAMINES

Despite a plethora of studies aimed at elucidating the optimal side-chain in phenylalkylamines (Biel, 1970), relatively few have been



(3.56) $R^1 = CH_3; R^2 = R^3 = H$

(3.57) $R^1 = R^2 = CH_3; R^3 = H$

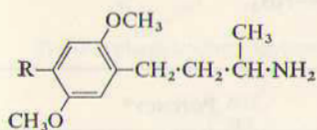
(3.58) $R^1 = R^3 = CH_3; R^2 = H$

(3.59) $R^1 = R^2 = R^3 = CH_3$

directed specifically to hallucinogenic activity. Nevertheless, it is clear that the integrity of the isopropylamine structure is essential for high potency. Thus, Shulgin (1963) described the α -alkyl derivatives of mescaline from methyl to nonyl, but only 3,4,5-trimethoxyamphetamine was more active than the natural hallucinogen; the higher homologues produced no psychic disturbances in man and were effective in disrupting mouse behaviour only at very high doses. The α -methyl group of amphetamine itself can be replaced by allyl, ethyl, or ethynyl groups of electron-donating character, without deleterious effects on centrally-mediated actions (Burger, Zimmermann, and Ariens, 1966; Shamano, Hitchens, Goldstein, and Beiler, 1968), but replacement by electron-withdrawing groups, such as cyano (Pinder, Burger, and Ariens, 1970) or trifluoromethyl (Pinder

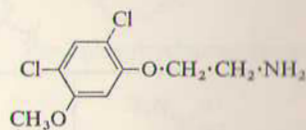
and Burger, 1967), abolishes amphetamine-like properties. Furthermore, α -trifluoromethyl derivatives of methoxylated phenylethylamines have little hallucinogenic activity, 2-amino-3-(3,4,5-trimethoxyphenyl)-1,1,1-trifluoropropane (3.55), for example, being only 0.11 times as potent as mescaline (Pinder, Brimblecombe, and Green, 1969).

The isopropylamine side-chain is clearly important, since movement of the α -methyl group to the β -position (3.56) or addition of extra methyl groups (3.57–3.59), reduces the hallucinogenic potency of DOM by an order (Aldous and others, 1974). The compounds also had a high degree of amphetamine-like activity in their pharmacological spectrum. Homoamphetamines, in which an extra methylene group has been inserted into the side-chain, are also very much less active than the corresponding amphetamines (Aldous and others,

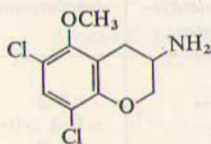


(3.60) R = OCH₃

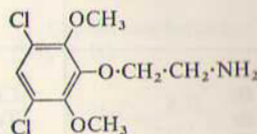
(3.61) R = CH₃



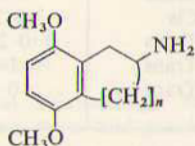
(3.62)



(3.63)



(3.64)



(3.65) n = 2

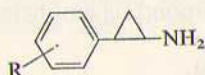
(3.66) n = 1

1974). Only two compounds showed hallucinogenic activity in rats, rabbits, and cats, the 2,4,5-trimethoxy- (3.60) and 2,5-dimethoxy-4-methyl-homoamphetamine (3.61) being respectively 0.001 and 0.01 times as potent as DOM in producing hyperthermia in rabbits. Addition of an oxygen atom to give the phenoxyethylamines was attended with more success. Several compounds were hyperthermic in animals and produced behavioural syndromes characteristic of hallucinogenic drugs (Julia and de Rosnay, 1969, 1970); 2,4-dichloro-5-methoxyphenoxyethylamine (3.62) was twice as potent as

mescaline in producing changes in the E.E.G. and E.CoG. of cats (Rougeul, 1969; Rougeul and Verdaux, 1972). Such LSD-like effects were not apparent, however, with the cyclic analogue (3.63) or 3,5-dichloro-2,6-dimethoxyphenoxyethylamine (3.64), emphasizing the importance of the free ethylamine side-chain and the 4-substituent. It will be interesting if such results can be extended to the phenoxyisopropylamines analogous to the amphetamines.

The requirement for a freely mobile alkylamine side-chain that is not held rigidly in a particular conformation is illustrated by studies

Table 3.8.—RELATIVE HALLUCINOGENIC POTENCIES OF SOME 2-PHENYL-CYCLOPROPYLAMINES



R	CONFORMATION	POTENCY*	
		<i>Relative to corresponding Phenylethylamine</i>	<i>Relative to corresponding Amphetamine</i>
4-Br	Cis	—	<0.3
4-Br	Trans	—	>0.4 >0.5
4-Cl	Cis	—	<0.2
4-Cl	Trans	—	>0.2 >0.3
3,4,5-(OCH ₃) ₃	Cis	<0.25†	<0.1‡
3,4,5-(OCH ₃) ₃	Trans	1.0-2.0†	<1.0‡
2,4,5-(OCH ₃) ₃	Trans	>1.6‡	0.8
2,5-(OCH ₃) ₂ -4-CH ₃	Trans	>0.5‡	0.36

*Hyperthermia in rabbits, except for those values marked (†) which were obtained in mice using muscle twitching as the measured parameter or in tests which involved disruption of schedule performance efficiency in rats (data from Walters and Cooper, 1968; Cooper and Walters, 1972; Aldous and others, 1974).

‡Extrapolated values using relative potency data in rodents from Tables 3.2-3.5.

with several cyclic compounds. 2-Amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (3.65), which is the cyclic analogue of 2,5-dimethoxyamphetamine, retains only the amphetamine-like effects of the parent compound and none of the hallucinogenic activity (Barfknecht, Nichols, Olesen, and Engelbrecht, 1971). Nevertheless,

both the parent compound, 2-amino-1,2,3,4-tetrahydronaphthalene (Barfknecht, Nichols, Rusterholz, Long, Engelbrecht, Beaton, Bradley, and Dyer, 1973), and its 7-hydroxy derivative (Green, Dressler, and Khazan, 1973), are claimed to be mescaline-like in rats. The more rigid indane derivative (3.66), which has not been described, might provide a more suitable analogy in view of the flexibility of the tetrahydronaphthalene moiety of 3.65. Certainly the 2-phenylcyclopropylamines (Table 3.8) showed hallucinogenic properties in animals superior to those of the corresponding phenylethylamines but less than those of the corresponding

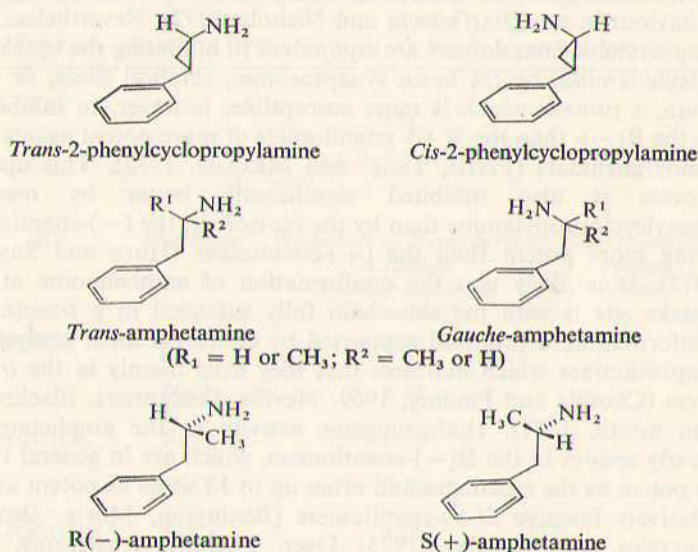


Fig. 3.4.—Stereochemical relationships between *cis*- and *trans*-2-phenylcyclopropylamines, *trans*- and *gauche*-amphetamines, and R(-)- and S(+)-amphetamines.

amphetamines (Walters and Cooper, 1968; Cooper and Walters, 1972; Aldous and others, 1974). 2-Phenylcyclopropylamines are potent inhibitors of monoamine oxidase (Burger, 1971) and their central activity may be a result of, at least in part, an enhanced resistance to biodegradation. They have not been reported in man as hallucinogenic agents despite a decade of clinical use of the parent compound as an anti-depressant under the name of Tranlycypamine or Parnate. The high potency in animal behavioural tests of the *trans*-isomer of 2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine suggests that it may be hallucinogenic in man.

The higher potency of the *trans*-isomers of hallucinogenic 2-phenylcyclopropylamines as compared to the *cis*-derivatives (Table 3.8) may reflect the stereochemical relationship of the former to the R(-)-enantiomers and *trans*-conformers of the corresponding amphetamines and of the latter to the S(+)-enantiomers and the *gauche*-conformers (Fig. 3.4). The S(+)-enantiomer of amphetamine itself is more potent than the R(-)- in producing central stimulation in animals and in inducing psychosis in man upon prolonged administration (Angrist, Shopsin, and Gershon, 1971), while S(+)-3,4-dimethoxyamphetamine was three times as active as its R(-)-enantiomer in disrupting conditioned avoidance response behaviour in rats (Barfknecht and Nichols, 1972). Nevertheless, the amphetamine enantiomers are equipotent in inhibiting the uptake of catecholamines by rat brain synaptosomes, cerebral slices, or striatum, a process which is more susceptible, however, to inhibition by the R(-)- than the S(+)- enantiomers of more potent agents like methylphenidate (Ferris, Tang, and Maxwell, 1972). This uptake process is also inhibited significantly better by *trans*-2-phenylcyclopropylamine than by the *cis*-isomer, the (-)-enantiomer being more potent than the (+)-enantiomer (Horn and Snyder, 1972). It is likely that the conformation of amphetamine at the uptake site is with the side-chain fully extended in a *trans*(anti)-conformation, a proposal supported by conformational analysis of amphetamines which indicates that they exist mainly in the *trans*-form (Chothia and Pauling, 1969; Neville, Deslauriers, Blackburn, and Smith, 1971). Hallucinogenic activity in the amphetamines clearly resides in the R(-)-enantiomers, which are in general twice as potent as the racemates and often up to 13 times as potent as the relatively inactive S(+)-enantiomers (Benington, Morin, Beaton, Smythies, and Bradley, 1973; Dyer, Nichols, Rusterholz, and Barfknecht, 1973; Aldous and others, 1974) (Table 3.9). It has now been confirmed that the R(-)-enantiomer of DOM is active in man at 8 µg./kg. (p.o.), a dose equivalent to twice its weight of racemate and with no effects for the S(+)-enantiomer at four times the dose (Shulgin, 1973b).

R(-)-2,5-dimethoxy-4-bromoamphetamine appears to be the most active amphetamine so far tested in animals, having about one-fifth of the potency of LSD in producing hyperthermia in rabbits; on a mg./kg. basis it is, of course, even more relatively effective, with almost one-half of the potency of LSD. The compound produces typical hallucinogenic signs at low doses in rats placed in the open field situation, in addition to E.E.G. patterns typical of LSD and those amphetamines known to be hallucinogenic in man. It is significant, however, that the parent racemate is reported not to be

hallucinogenic in man, producing only enhanced perception and slight euphoria (Shulgin and others, 1971). Nevertheless, DOM and DOET share this property at low doses, and the former at least is known to be a potent hallucinogen at higher doses. Perhaps higher doses of 2,5-dimethoxy-4-bromoamphetamine will also prove to be hallucinogenic.

4. PHENETHANOLAMINES

Many hallucinogenic drugs, be they phenylethylamines or not, have sympathomimetic properties, and there have been suggestions from

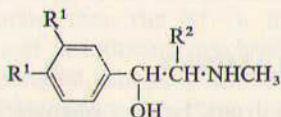
Table 3.9.—RELATIVE POTENCIES OF R(–)– and S(+)-AMPHETAMINES

$ \begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_4\text{---CH}_2\text{---CH---NH}_2 \\ \\ \text{R} \end{array} $			
R	Enantiomer	Production of Hyperthermia in Rabbits (Potency relative to Racemate)*	Enantiomeric† Potency Ratio
2,5-(OCH ₃) ₂	R(–)	2.32	5.0
	S(+)	0.51	
3,4,5-(OCH ₃) ₃	R(–)	1.79	8.5
	S(+)	0.21	
2,4,5-(OCH ₃) ₃	R(–)	2.02	12.6
	S(+)	0.16	
2,5-(OCH ₃) ₂ -4-CH ₃	R(–)	1.80	10.2
	S(+)	0.177	
2,5-(OCH ₃) ₂ -4-Br	R(–)	1.73	12.2
	S(+)	0.14	

*All active compounds produced hallucinogenic profiles in behavioural tests in rats and in the cat E.E.G. Reference should be made to Tables 3.3–3.5 for the absolute activities of the racemates.

†The enantiomeric potency ratio may not necessarily correspond exactly to the ratio of activities, because of differences in methods of calculation.

time to time that the classical drugs of this type, such as adrenaline (3.67) or ephedrine (3.68), are hallucinogenic. Certainly, adrenaline, given intravenously in doses larger than those normally used in therapeutic practice, causes fear, anxiety, and tension in both normal and neurotic subjects (Lindemann, 1935; Altschule, 1954).



(3.67) $R^1 = OH$; $R^2 = H$

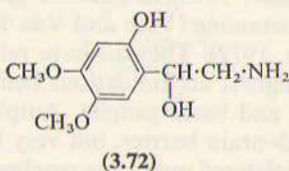
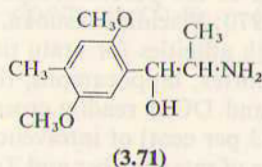
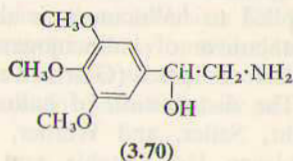
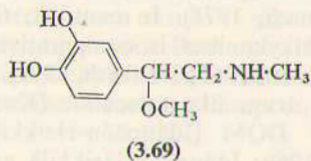
(3.68) $R^1 = H$; $R^2 = CH_3$

A similar symptomatology is produced by ephedrine or noradrenaline, although the latter is much less potent in this respect (Swan, 1952). Hoffer and Osmond (1967) have designated these model neuroses as being due to any chemical which in non-toxic doses produces anxiety or tension in the absence of changes in perception or thought. The chief changes are in the areas of affect, mood, interest, and drive, and are produced by most hallucinogens when given in small doses. However, the gross alterations in perception and thought which characterize the action of hallucinogens are not observed with drugs like adrenaline or ephedrine. Various alkaloids of the ephedrine family occur naturally in the drug *khat*, which is masticated in the Middle East and East Africa for its euphoriant properties and is derived from *Catha edulis*.

Adrenaline methyl ether (3.69) was originally designed as a substitute for adrenaline with reduced autonomic activity. It has, in fact, only 1/300 the blood-pressure elevating effect of the parent compound but retains 1/10 the central stimulant effect (Page and Hoffer, 1964; Hoffer and Osmond, 1967). It can therefore be given in large doses without producing cardiovascular effects, and has proved to be a useful psychic stimulant in depressed patients. There is no evidence that even large doses produce hallucinations, and its classification together with the hallucinogens (Hoffer and Osmond, 1967) is not warranted on present evidence.

A large number of analogous compounds, with or without the alkyl group on the alcoholic hydroxyl, have been examined without evidence of any hallucinogenic properties (Usdin and Efron, 1967). Even the ethanolamine analogues of mescaline, 3,4,5-trimethoxyphenethanolamine (3.70), and of DOM, 2,5-dimethoxy-4-methylphenopropanolamine (3.71) produced only amphetamine-like effects in animals (Friedman, Parameswaran, and Burstein, 1963; Aldous and others, 1974). It seems likely therefore that the proposal by

Shulgin and his colleagues (1969) that the endogenous psychotogen of schizophrenia is 2-hydroxy-4,5-dimethoxyphenethanolamine



(3.72) will ultimately prove untenable when the compound is evaluated pharmacologically.

III. FACTORS AFFECTING THE POTENCY OF HALLUCINOGENIC PHENYLALKYLAMINES

It is clear from the extensive analyses of structure-activity relationships that certain generalities can now be made regarding the optimal structural requirements for high hallucinogenic potency in the phenylalkylamine series. These are:

1. An isopropylamine side-chain, containing a primary amino group and in which the configuration at the α -carbon atom is R.

2. 2,4,5-Trisubstitution in the benzene ring, preferably with methoxy groups in the 2- and 5- positions and a substituent at position 4 which is resistant to metabolic degradation. This substituent should be no larger than bromo or N-propyl.

Such considerations adequately predict the potential hallucinogenic activity of any phenylalkylamine, all other factors being equal. However, it is clear that other factors must play a role in determining overall potency; two of the most important being metabolism and transport to the site of action. Little information is available regarding lipid solubilities and other properties associated with the transport of phenylalkylamines into the central nervous system; indeed, until such information is available, together with more

accurate pharmacological tests, it seems unlikely that the quantitative mathematical analyses of structure-activity relationships due to Hansch or to Free and Wilson will prove predictively useful when applied to hallucinogenic drugs (Hansch, 1971). In contrast, the metabolism of hallucinogenic phenylalkylamines is comparatively well documented (Giarman and Freedman, 1965; Nieforth, 1971).

The distribution of hallucinogenic drugs like mescaline (Korr, Lehr, Seiler, and Werner, 1969) or DOM (Idänpään-Heikkilä, McIsaac, Ho, Fritchie, and Tansey, 1969; Idänpään-Heikkilä and McIsaac, 1970) in animals parallels that of the parent compound, amphetamine (Vree and Van Rossum, 1970; Placidi, Masuoka, and Earle, 1972). They all have relatively high affinities for brain tissue, the highest accumulations being in the cortex, hippocampus, thalamus, and basal ganglia. Amphetamine and DOM readily cross the blood-brain barrier, but very little (<0.2 per cent) of intravenously administered mescaline reaches the brains of rats (Denber and Teller, 1970); this transport difference may be reflected in the higher potency of DOM as compared to the natural hallucinogen, since the half-lives of the drugs in the brain are very similar. It is interesting that chlorpromazine, regarded as a hallucinogen antagonist, actually enhances the accumulation of mescaline into the brains of mice (Shah and Gibson, 1973).

The influence of structural changes among phenylalkylamines upon their biotransformations has been extensively reviewed (Beckett and Brookes, 1970; Boissier, Hirtz, Dumont, and Gerardin, 1970; Smith and Dring, 1970; Beckett, Van Dyk, Chissick, and Gorrod, 1971), and the possible routes are indicated in *Fig. 3.5*. Four general pathways are available: (a) oxidative deamination to the ketone or aldehyde followed by further oxidation to the acid or reduction to the carbinol; (b) aromatic hydroxylation to the corresponding 4-hydroxy derivative which may be excreted in part unchanged and as its O-glucuronide conjugate; (c) β -hydroxylation to the corresponding phenylpropanolamine compound; and (d) N-dealkylation of N-substituted phenylalkylamines to the primary amine. Some phenylalkylamines are relatively inert metabolically and are excreted substantially unchanged, while recent work with amphetamines suggests that oximes can arise via N-oxide intermediates (Beckett and others, 1971). The particular route which is favoured for any one drug varies greatly with the species, although all may be used to different degrees; amphetamine is probably the most widely documented example (Smith and Dring, 1970; Caldwell, Dring, and Williams, 1972) (*Table 3.10*). It is clear that care must be exercised in extrapolating metabolic routes derived in experimental animals to those which obtain in man.

Phenylethylamines are metabolized chiefly by oxidative deamination, and the generally greater resistance of the amphetamines to the action of amine oxidases is reflected in their higher hallucinogenic potency as a result of greater penetration to central sites (Hellot, Lauquin, and Pacheco, 1970). Certainly, many methoxylated phenylethylamines, such as the 2,3- and 3,4-dimethoxy derivatives and the 4-methoxy compound, which are not hallucinogenic *per se*,

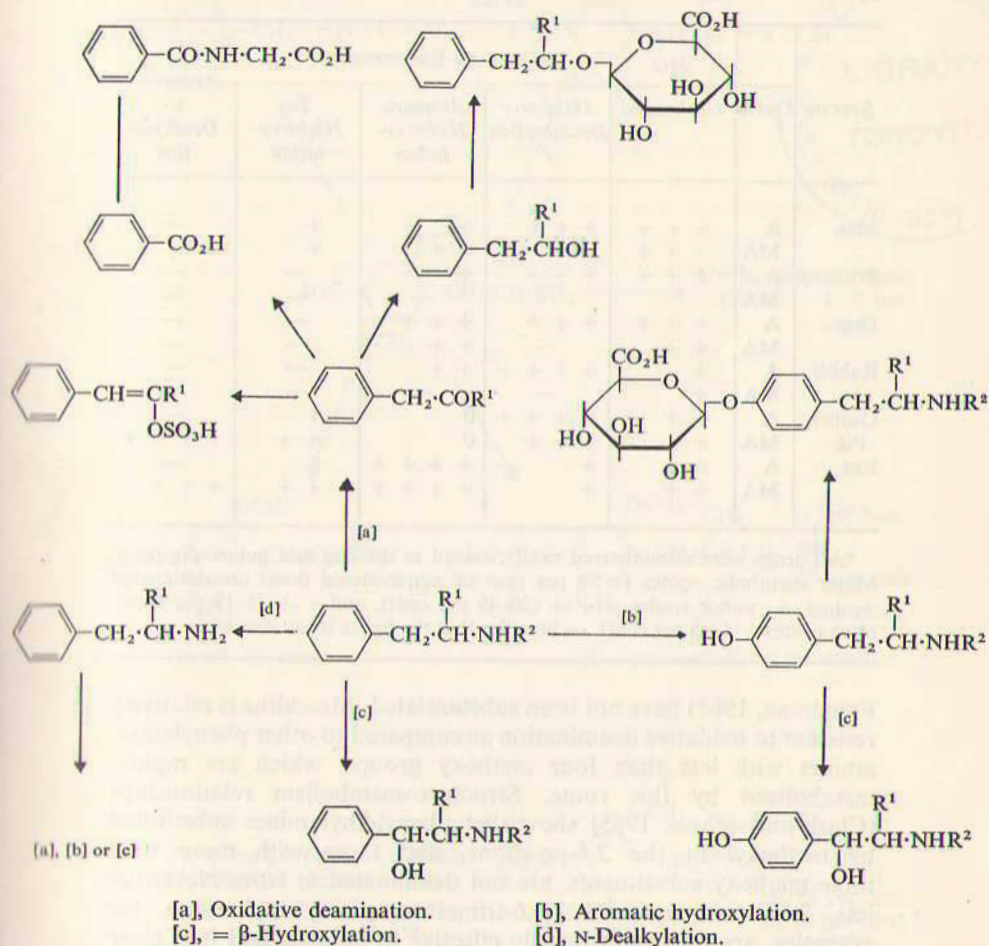


Fig. 3.5.—Possible metabolic routes for phenylalkylamines. All may be used to varying degrees depending upon the species and the particular compound.

produce hallucinogenic profiles in animals pretreated with amine oxidase inhibitors (Smythies and others, 1969). The metabolism of mescaline has already been discussed in Section 3.I, and it is sufficient to note here that suggestions that its activity was due to metabolic products of oxidative deamination (Giarman and

Table 3.10.—COMPARATIVE METABOLISM OF AMPHETAMINE (A) AND N-METHYL-AMPHETAMINE (MA) (data from Smith and Dring, 1970; Caldwell and others, 1972)

SPECIES	DRUG	URINARY EXCRETION*				
		Unchanged	Oxidative Deamination	Aromatic Hydroxy- lation	β - Hydroxy- lation	N- Dealkyla- tion
Man	A	+++	+++	+	+	—
	MA	+++	++	++	+	++
Primates	A	+++	+++	+	—	—
	MA	—	—	—	—	—
Dog	A	+++	+++	+++	—	—
	MA	++	—	++	—	—
Rabbit	A	+	++++	++	—	—
	MA	+	—	—	—	—
Guinea Pig	A	++	++++	0	+	—
	MA	+	+++	0	++	++++
Rat	A	++	+	++++	+	—
	MA	++	+	++++	++	+++

*All drugs were administered orally, except in the dog and guinea-pig (i.p.). Major metabolic routes (>50 per cent of administered dose) are designated + + + +, minor routes + + + (20-49 per cent), and + + (5-19 per cent), trace routes + (<5 per cent). — Signifies that the figure is not available.

Freedman, 1965) have not been substantiated. Mescaline is relatively resistant to oxidative deamination as compared to other phenylethylamines with less than four methoxy groups, which are rapidly metabolized by this route. Structure-metabolism relationships (Clark and others, 1965) show that phenylethylamines substituted by methoxyl in the 2,6-positions, and those with more than three methoxy substituents, are not deaminated *in vitro*. Nevertheless, 2,6-dimethoxy- and 2,3,6-trimethoxy-phenylethylamines, for examples, are not behaviourally effective in animals and it is clear that resistance to metabolic degradation must be accompanied by correct structural complementarity to the central receptor if hallucinogenic effects are to be observed.

The proposal has been made that in view of the bioinactivation of amphetamine itself by aromatic hydroxylation it is likely that hallucinogenic phenylalkylamines containing a 4-methoxy substituent are demethylated *in vivo* (Shulgin and others, 1969). Certainly, demethylation of 3,4-dimethoxyphenylethylamine occurs at the 4-position at a rate 15 times that of demethylation at the 3-position

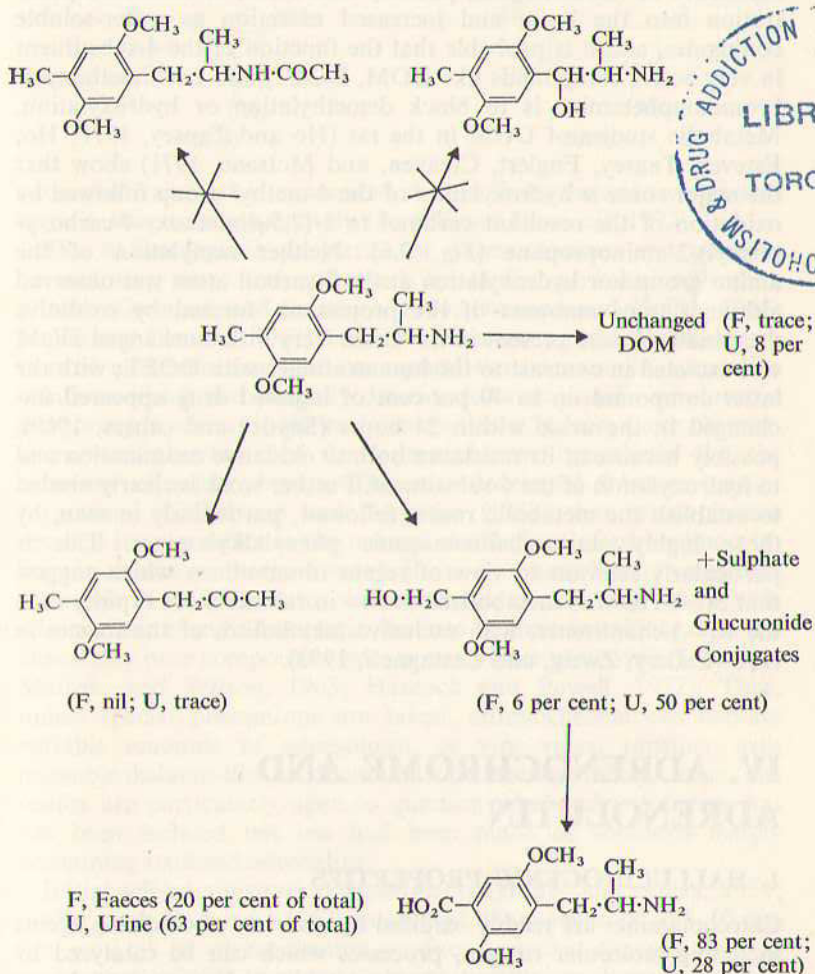


Fig. 3.6.—Metabolism of 2,5-dimethoxy-4-methylamphetamine (DOM) in the rat following a dose of 5 mg./kg. (i.p.) (data from Ho, Estevez, and others, 1971). (The method used radioactive DOM and the figures may not necessarily total 100 per cent.)

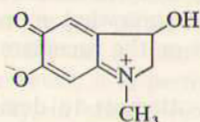
(Sargent, Israelstam, Shulgin, Landaw, and Finley, 1967). It is interesting that preliminary studies suggest that the drug is demethylated in the 4-position faster by acute schizophrenics but slower by chronic subjects when compared to normal controls upon intravenous administration (Tozman, Schweitzer, and Friedhoff, 1972). Hydroxylated phenylethylamines or amphetamines are ineffective as hallucinogens, possibly as a result of decreased penetration into the brain and increased excretion as water-soluble conjugates, and it is probable that the function of the 4-substituent in very active compounds like DOM, DOET, and 2,5-dimethoxy-4-bromoamphetamine is to block demethylation or hydroxylation. Metabolic studies of DOM in the rat (Ho and Tansey, 1971; Ho, Estevez, Tansey, Englert, Creaven, and McIsaac, 1971) show that the major route is hydroxylation of the 4-methyl group followed by oxidation of the resultant carbinol to 1-(2,5-dimethoxy-4-carboxyphenyl)-2-aminopropane (Fig. 3.6). Neither acetylation of the amino group nor hydroxylation at the β -carbon atom was observed although trace amounts of the propanone, formed by oxidative deamination, were present in the urine. Very little unchanged DOM was excreted in contrast to the human studies with DOET; with the latter compound up to 40 per cent of ingested drug appeared unchanged in the urine within 24 hours (Snyder and others, 1969), possibly because of its resistance both to oxidative deamination and to hydroxylation of the 4-substituent. Further work is clearly needed to establish the metabolic routes followed, particularly in man, by those highly active hallucinogenic phenylalkylamines. This is particularly relevant in view of recent observations which suggest that S(+)-DOM is metabolized *in vivo* in rabbits more rapidly than the R(-)-enantiomer, with exclusive metabolism of the former *in vitro* (Callery, Zweig, and Castagnoli, 1973).

IV. ADRENOCHROME AND ADRENOLUTIN

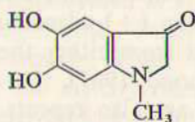
1. HALLUCINOGENIC PROPERTIES

Catecholamines are readily oxidized by a variety of oxidizing agents including molecular oxygen, processes which can be catalyzed by metals, enzymes, and irradiation, or which often proceed in an autoxidative manner (Heacock and Powell, 1972). Adrenochrome (3.73), the red oxidation product of adrenaline, is the best known member of the family of red-to-violet coloured indoline-5,6-quinones,

known collectively as the 'aminochromes'. Such compounds often cause problems in the storage of catecholamine solutions, and adrenochrome, for example, can undergo further rearrangement in alkaline solution to the intensely yellow-green fluorescent compound, adrenolutin (3.74). Though often formulated as the indoline-5,6-quinone and the 3,5,6-trihydroxyindole, adrenochrome and



(3.73)



(3.74)

adrenolutin are better represented chemically by the zwitterionic and ketonic structures respectively (Powell and Heacock, 1972).

The hallucinogenic properties of adrenochrome, and possibly adrenolutin, were first suspected by Hoffer and his colleagues (Hoffer, Osmond, and Smythies, 1954; Osmond and Hoffer, 1958; Hoffer and Osmond, 1967), based on observations of self-administration of adrenochrome and on reports that the use of adrenaline solutions which had partially deteriorated occasionally produced a temporary psychosis in the recipient patients. Indeed, these observations were the basis of the 'adrenochrome hypothesis' for the aetiology of schizophrenia. This was developed from an earlier suggestion of Osmond and Smythies (1952) that schizophrenia resulted from a defect in the normal metabolism of adrenaline with formation of a psychotoxic metabolite *in vivo*, namely adrenochrome. However, it is difficult to evaluate much of the early work with adrenochrome and adrenolutin because of their instability, and the chemically pure compounds were not available until 1963 (Heacock, Mattok, and Wilson, 1963; Heacock and Powell, 1972). Thus, unless special precautions are taken, adrenochrome can contain variable amounts of adrenolutin, or vice versa, together with insoluble melanin-like products and some residual metallic ions. The results are particularly open to question where adrenochrome has not been isolated but use had been made of solutions merely containing oxidized adrenaline.

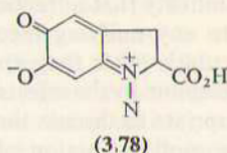
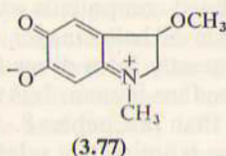
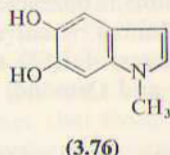
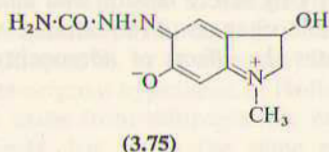
Initial self-administration experiments (Hoffer and others, 1954; Hoffer and Osmond, 1967) suggested that doses of 0.5–10 mg. (s.c. or i.v.) of adrenochrome produced psychic changes such as preoccupation with inanimate objects, negativism, loosening of the associative process, anxiety, and distractability. These results were confirmed in mental patients who received intravenous injections of the same solutions as those used by Hoffer's group, though higher

doses of 50–100 mg. were used (Schwarz, Wakim, Bickford, and Lichtenheld, 1956). Solid adrenochrome produced much the same symptomatology in man, sublingual doses of 3 mg. causing psychic changes within 10 minutes, with marked disturbances of visual perception, particularly colour and shape (Taubmann and Jantz, 1957). Depression was more frequently reported than euphoria in all these experiments, and it is interesting that adrenochrome prepared from (+)-adrenaline appears to be somewhat more potent than that from either the (–)-enantiomer or the racemate (Hoffer and Osmond, 1967).

There are also reports of unsuccessful attempts to demonstrate the psychotomimetic effects of adrenochrome in man (Rinkel and Solomon, 1957; Smythies, 1960). The apparent ambiguity of the results undoubtedly lies in the use of different samples of adrenochrome, prepared by different procedures, of variable purity, and often containing trace quantities of other psychoactive contaminants. The most extensive studies are due to a group of workers in Czechoslovakia (Grof, Vojtechovsky, Vitek, and Frankova, 1963), who observed qualitative and quantitative differences when synthetic or commercially available adrenochrome was used. Double-blind studies in normal subjects and in psychiatric patients, including some who were already experienced with LSD, mescaline, and psilocybin, demonstrated definite psychotic reactions and only one of those who received placebo, a red dye, reported any psychic changes. It was concluded that high doses of adrenochrome caused transitory psychotic episodes while lower doses gave rise to neurotic and uncertain reactions. The Czech workers concluded that the drug produced an approximate model of subtle schizophrenic alteration in the area of associative thinking. These results were subsequently reproduced by the use of pure crystalline adrenochrome prepared according to the methods of Heacock and his co-workers (Hoffer and Osmond, 1967). It is clear that adrenochrome, though not producing the visual and auditory hallucinations associated with the use of LSD or mescaline, is to be classified with them because of the characteristic changes in thought and mood without any loss of consciousness. The effects of adrenochrome are more insidious than those of the classical hallucinogens and can last for several days.

The chemical instability of adrenochrome led to the investigation of the properties of its monosemicarbazone derivative (3.75, adrenoxyl), a drug widely used as a haemostatic agent. Early studies by Hoffer's group suggested that it was euphoriant (Hoffer and Osmond, 1967), a view confirmed in patients who received the drug for haemostatic purposes; they were very happy, uncomplaining, and had a more pleasant post-operative course even after dental

surgery. Carefully-controlled double-blind studies showed that adrenoxyl produced the subjective sensations of a stimulant drug and the performance effects of a depressant, patients feeling happy and euphoric but performing poorly on simple mental tasks (Hoffer and Osmond, 1967). It is hardly surprising that adrenoxyl fails to show psychic properties similar to the parent adrenochrome, because there is no evidence that the latter is regenerated *in vivo* from its semicarbazone either in rodents (Sohler, Noval, Pellerin, and Adams, 1967) or in man (Fischer and Lecomte, 1948; Stewart, 1970). However, it is pertinent that one of the urinary metabolites of adrenoxyl in man is 5,6-dihydroxy-N-methylindole (3.76), which



has been used to reduce tension and anxiety in otherwise normal subjects (Hoffer and Osmond, 1960). The indole appears to have no hallucinogenic properties, although it does affect mood (Hoffer and Osmond, 1967), and it is also ineffective in animal behavioural tests (Taborsky, 1968). In this respect, it resembles other compounds in which the 3-hydroxy group of adrenochrome is absent, or in those where it is blocked, as in adrenochrome methyl ether (3.77). Nevertheless, it is not known whether other aminochromes, with or without the 3-hydroxy group, are psychotomimetic, although the widespread occurrence of untoward behavioural effects associated with L-dopa therapy in Parkinsonism (Pinder, 1972) has led to suggestions (Rizzoli and Galzigna, 1971) that psychotic reactions are produced by the cyclization product, dopachrome (3.78).

Adrenolutin also causes psychological changes in man when given in oral doses of 25–50 mg. (Hoffer and Osmond, 1967). The drug appears to be as active as adrenochrome, but produces fewer perceptual changes and with a longer recovery time. Adrenolutin

induces, in normal subjects, clear evidence of thought disorder, with decreased anxiety, decreased insight into these changes, affective disharmony, and some subtle somatic changes. The major feature of its symptomatology is the thought disorder, marked by decreased ability towards abstraction, inability to solve problems and proverbs, combined with changes in mood and a marked resemblance to the disorders of thought without the perceptual changes seen in schizophrenia. There are doubts as to the purity of the adrenolutin used in these studies (Hoffer and Osmond, 1967), and the possible hallucinogenic actions of adrenolutin remain to be confirmed. Nevertheless, both adrenolutin and adrenochrome potentiate the effects of LSD, particularly if the reaction to the latter alone is characterized primarily by severe tension and anxiety with minimal visual and psychedelic changes. Pretreatment with small doses of LSD also potentiates the effects of adrenochrome (Hoffer and Osmond, 1967).

2. MODE OF ACTION

It is unlikely that adrenochrome and related compounds will readily fit into any unifying theory for the mode of hallucinogenic action, particularly since they appear to differ greatly from drugs like LSD or mescaline in the effects which they produce in man. It is therefore appropriate to discuss them here rather than in Chapter 8.

The mode of action of adrenochrome is intimately related to its possible involvement in mental illness, particularly schizophrenia, as an endogenous psychotogen. The role of aminochromes as intermediates in the *in vivo* formation of melanin pigments has long been recognized, while many mammalian tissues oxidize adrenaline to adrenochrome *in vitro* (Hoffer and Osmond, 1967; Heacock and Powell, 1972). However, the presence of adrenochrome in mammalian tissues *in vivo* has not been unambiguously demonstrated, possibly in view of the transient existence of the compound resulting from its high chemical reactivity. It is possible that reversible formation of relatively stable addition products with other molecules, especially those containing sulphydryl groups, could temporarily stabilize adrenochrome *in vivo*. Indeed, this concept has formed the basis of several hypotheses as to the aetiology of mental disturbances.

Caeruloplasmin, a copper protein enzyme present in serum, is capable of oxidizing adrenaline and other catecholamines to aminochromes, although it probably plays little part in man (Heacock and Powell, 1972). Nevertheless, caeruloplasmin levels are elevated in schizophrenia and the enzyme has been used in the treatment of the disease (Hoffer and Osmond, 1967). Furthermore, the potentiating

effect of LSD-pretreatment on the psychotomimetic actions of adrenochrome and adrenolutin, and vice versa, is inhibited by caeruloplasmin, as is the hallucinogenic action of LSD alone. This has led to suggestions that caeruloplasmin forms part of a protective system whose function is to protect the body against amines and their metabolites liberated during stress; certainly, the enzyme binds irreversibly to adrenolutin, a process which would accelerate the catabolism of psychotoxic adrenochrome (Hoffer and Osmond, 1967). In this context, it is interesting that Barrass and Coult (1972) have shown that, at least *in vitro*, the caeruloplasmin-catalyzed oxidation of serotonin is inhibited by hallucinogens but that of noradrenaline is accelerated. This process, if reproduced centrally *in vivo*, would lead to elevated brain levels of serotonin, a finding characteristic of hallucinogenic drugs (Brawley and Duffield, 1972; see Chapter 8), or to increased levels of adrenochrome as suggested in the original hypothesis of Hoffer and others (1954). It is significant that urine from schizophrenic patients, but not that from normal subjects, has much the same effect on caeruloplasmin-catalyzed oxidations of noradrenaline and serotonin *in vitro* as do the hallucinogens (Barrass, Coult, Drysdale, and Marjot, 1970).

Other adrenaline-oxidizing systems have been detected in human blood serum and plasma (Heacock and Powell, 1972), but it is unlikely that the levels of such factors are elevated in schizophrenia (Altschule and Nayak, 1971). Adrenaline-oxidizing activity is also present in rat brain, and serotonin is capable of either inhibiting or accelerating the formation of adrenochrome by this system, depending upon the relative concentrations of noradrenaline and serotonin (Vanderwende and Johnston, 1970). Serotonin interacts with various catecholamines to form a complex and it is suggested that such an interaction might assist in modulating the activities of brain catecholamines. Thus, in conditions of lowered serotonin concentrations in the brain the excess noradrenaline would lead to accelerated formation of the psychotoxic adrenochrome. It is also significant that adrenochrome is itself capable of activating adrenaline-oxidizing enzymes isolated from various muscles, including brain, and particularly those containing high levels of the catecholamine (Inchiosa, 1967; Inchiosa and Rodriguez, 1969). It is therefore possible that exogenously administered adrenochrome could result in an autocatalytic oxidation of adrenaline.

Complex formation has also been implicated in the recent 'short circuit' theory of mental illness (Galzigna, 1970; Galzigna and Rizzoli, 1970), based upon observations that acetylcholine and noradrenochrome formed stable complexes under physiological conditions. According to the theory, if a central catecholamine were

leaking from a synapse, in the absence of the enzyme system which normally destroys it, then it could be oxidized to the aminochrome, which then forms a stable complex with acetylcholine. Thus, the psychotoxic aminochrome is stabilized and the acetylcholine protected from destruction by acetylcholinesterase, hence the concept of a 'short circuit' between the catecholaminergic and cholinergic systems. Increased levels of aminochromes might therefore be responsible for the onset of mental illness, while exogenously administered adrenochrome could have such prolonged effects in man because of its stabilization by complex formation. Chlorpromazine, which is effective both in schizophrenia and in alleviating the hallucinogenic experience, also interacts with adrenochrome to produce a complex even more stable than that formed between adrenochrome and acetylcholine (Galzigna, 1972). It is not clear whether the latter might act as a stable reservoir for adrenochrome or whether it would *per se* be an irritant focus at the cortical level by inducing aberrant synaptic communication. The mode of action of adrenochrome at the molecular or the neurophysiological level remains largely unresolved.

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Chapter 4

Indolealkylamines and Related Compounds

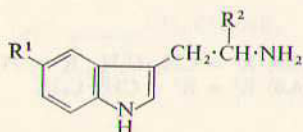
THE largest group of naturally occurring hallucinogenic substances is undoubtedly represented by those whose structure is indolic, including such compounds as the tryptamines, the ergot and harmala alkaloids, ibogaine, and yohimbine. Their presence in intoxicating beverages, snuffs, and edible materials is widespread throughout Central and South America and much of the rest of the world, and is discussed in Chapter 1. The collective term *indolealkylamines* has come to include those compounds which contain a 3-(2-aminoethyl)-indole moiety in their structure, a feature common to most of the indolic hallucinogens and to the central neurotransmitter 5-hydroxy-tryptamine (Airaksinen and McIsaac, 1968; Van Praag, 1970).

Knowledge of the hallucinogenic properties of natural indolic substances prompted investigation of a large number of synthetic analogues, though the most potent, lysergic acid diethylamide, was originally developed as a potential oxytocic and only later were its central effects discovered by accident. Nevertheless, synthetic difficulties have precluded the type of extensive investigation of structure-activity relationships associated with the phenylethylamines, particularly for the complex alkaloids of the ergot family. Indeed, such relationships are virtually restricted to those compounds of relatively simple structure, namely the tryptamines.

I. TRYPTAMINES

Tryptamine itself (4.1) is probably not hallucinogenic. It produces mainly autonomic effects when given intravenously to man (Martin and Sloan, 1970) or animals (Hoffer and Osmond, 1967); the only central symptoms reported in man were changes in hearing and

vision together with light-headedness and euphoria. Similar effects have been noted following ingestion of the precursor amino-acid tryptophan (4.2) (Olsen, Gursay, and Vester, 1960; Smith and Prockop, 1962; Hoffer and Osmond, 1967), while neither 5-hydroxytryptamine (4.3) nor 5-hydroxytryptophan (4.4) produces prominent behavioural changes in animals or man. Nevertheless, tryptamine, in producing such central effects in man, may interact with receptors responsible for mediating the hallucinogenic effects of lysergic acid diethylamide, since cross-tolerance exists between the two in animals (Martin and Eades, 1972).



(4.1) $R^1 = R^2 = H$

(4.2) $R^1 = H; R^2 = CO_2H$

(4.3) $R^1 = OH; R^2 = H$

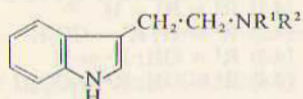
(4.4) $R^1 = OH; R^2 = CO_2H$

Hallucinogenic activity in the tryptamine series is dependent upon suitable substitution of the ethylamine side-chain, and is often further enhanced by hydroxylation or methoxylation of the aromatic ring. N-Acylation of tryptamine and its congeners, which occurs *in vivo* as part of the biosynthesis of melatonin, does not confer hallucinogenic properties on the molecules; indeed, the reverse is often the case since a number of N-acyltryptamines possess depressant action in the central nervous system (Von Strandtmann, Puchalski, and Shavel, 1964; Ho, An, Noel, and Tansey, 1971). In contrast, N,N-dialkylation, but not generally N-monoalkylation, leads to tryptamines with pronounced hallucinogenic effects.

1. N-MONOALKYLTRYPTAMINES

N-Monoalkyltryptamines resemble the unsubstituted tryptamines in being good substrates for amine oxidases (Erspamer, 1955), a property which is reflected in their relatively poor hallucinogenic activity as compared to their N,N-dialkyl analogues. Thus, neither tryptamine nor its N-methyl derivative, both of which are oxidatively deaminated in rats to free (and conjugated) indole-3-acetic acids to the extent of 84.6 and 35.7 per cent respectively, produce behavioural changes in animals or man, whereas N,N-dimethyltryptamine, which is but little affected by amine oxidases, is a potent hallucinogen. The same relationship holds with the 5-methoxy derivatives, the N-methyl compound and the parent tryptamine being metabolized by amine oxidases to an extent greater than 80 per cent (Kveder and McIsaac, 1961; Taborsky and McIsaac, 1964a) and being

ineffective in altering animal behaviour (Smythies, Bradley, and Johnston, 1967), while 5-methoxy-N,N-dimethyltryptamine is resistant to oxidative deamination and is among the most potent of the hallucinogenic tryptamines. Nevertheless, behavioural changes are produced in animals by tryptamines which contain relatively bulky N-substituents (Brimblecombe, 1967), the most potent being N-benzyltryptamine (4.5); this compound was effective in raising rabbit rectal temperature at a dose three times that of N,N-dimethyltryptamine and it also induced LSD-like behaviour in rats placed in the open field situation at doses of 0.5 mg./kg. (s.c.). The drug has not been tested in man and nothing is known about its metabolism.



(4.5) $R^1 = \text{CH}_2 \cdot \text{C}_6\text{H}_5$; $R^2 = \text{H}$

(4.6) $R^1 = R^2 = \text{CH}_2 \cdot \text{C}_6\text{H}_5$

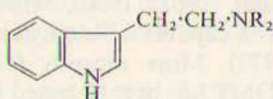
It may well be comparatively resistant to oxidative deamination, although it is odd that the corresponding N,N-dibenzyl derivative (4.6), which is more toxic than the monobenzyl compound, is virtually inactive in these behavioural situations. Possibly the molecule is too bulky to fit easily to a potential hallucinogenic receptor.

2. N,N-DIALKYLTRYPTAMINES WITHOUT ARYL SUBSTITUENTS

While resistance to rapid bioinactivation by amine oxidases is clearly important in determining overall potency of the N,N-dialkyltryptamines it is also evident that other factors must play a role since tryptamine and N-methyltryptamine, for examples, do not produce the behavioural changes characteristic of the N,N-dialkyltryptamines even in animals pretreated with inhibitors of monoamine oxidase (Hoffer and Osmond, 1967). Nevertheless, indole-3-acetaldehydes, which are intermediates in the metabolism of tryptamines to indole-3-acetic acids (Weissbach, Redfield, and Udenfriend, 1957), have effects on the central nervous system and apparently play a role in the modulation of sensory function and in the mechanisms of sleep (Sabelli, Giardina, Alivisatos, Seth, and Ungar, 1969; Sabelli and Giardina, 1970; Sabelli, Giardina, and Alivisatos, 1970). It is not inconceivable that similar aldehydes might also be involved in the production of sensory and perceptual disturbances.

N,N-Dimethyltryptamine (DMT, 4.7) occurs widely, though rarely as the major indolic constituent, in many South and Central American plants, such as *Piptadenia* and *Virola* species and *Mimosa*

hostilis, from which are made various hallucinogenic snuffs (Holmstedt and Lindgren, 1967; Saxton, 1968a) (see Chapter 1). Its isolation from such sources undoubtedly led to the unusual situation of the human studies with the drug being carried out several years before many of those in animals. The effective dose in man is approximately 1 mg./kg. intramuscularly and the drug is also effective when snuffed or smoked, but is inactive orally even in doses as high as 350 mg. (Szára, 1956, 1961b; Arnold and Hofmann, 1957; Böszörményi and Szára, 1958; Sai-Halasz, Brunecker, and Szára,



(4.7) $R = \text{CH}_3$

(4.8) $R = \text{C}_2\text{H}_5$

(4.9) $R = n\text{-C}_3\text{H}_7$

(4.10) $R = \text{CH}_2\text{-CH}=\text{CH}_2$

(4.11) $R = n\text{-C}_4\text{H}_9$

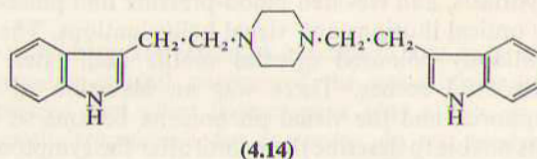
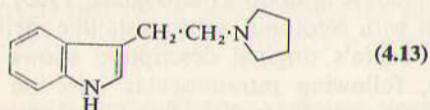
(4.12) $R = n\text{-C}_6\text{H}_{13}$

1958; Turner and Merlis, 1959). The hallucinogenic effects set in rapidly and fade away within an hour, and are diminished by pretreatment with monoamine oxidase inhibitors (Sai-Halasz, 1963) but potentiated by pretreatment with serotonin antagonists like methysergide (Sai-Halasz, 1962). Szára's original description shows an onset within 3–4 minutes, following intramuscular injection of 75 mg. of DMT, of autonomic changes such as trembling, nausea, mydriasis, and elevated blood-pressure and pulse-rate, accompanied by optical illusions and visual hallucinations. The latter consisted of brilliantly coloured oriental motifs and, later, rapidly changing wonderful scenes. There was an elevation of mood leading to euphoria, and the visual phenomena became so intense that Szára was unable to describe them until after the symptoms had disappeared (45–60 minutes).

Other N,N -dialkyltryptamines produce similar effects to DMT in man, though their persistence is somewhat greater, with hallucinations lasting for up to 3 hours (Szára and Hearst, 1962). These include the N,N -diethyl (DET, 4.8), N,N -dipropyl (4.9), and N,N -diallyl (4.10) compounds, none of which are found in nature. The N,N -dibutyl derivative (4.11) showed a considerable decrease in activity, while increasing the chain length to N,N -dihexyl (4.12) abolished hallucinogenic effects in man (Szára, 1961b). DET received an extended trial in 30 normal subjects and 41 psychiatric subjects, where it was reported to be more satisfactory than LSD or mescaline in increasing communication and facilitating therapy because of its shorter duration of action (Böszörményi, Der, and Nagy, 1959). Administration (i.m.) of 0.7–0.8 mg./kg. produced a mescaline-like

syndrome of moderate severity, with prominent perceptual and mood changes but with a clouding of consciousness that was likened by many subjects to being drunk, half-asleep, or febrile. After-effects included headache, depression, and insomnia, which rarely lasted for more than 24 hours. Other studies confirm these findings (Szára, Rockland, Rosenthal, and Handlon, 1966).

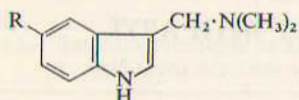
It is interesting that schizophrenic patients show a markedly reduced response to DMT or DET with no hallucinations, suggesting a pre-existing condition of tolerance to the tryptamines (Hoffer and Osmond, 1967). DMT and its 5-hydroxy derivative, bufotenin, have been detected in the urine from schizophrenic subjects (Tanimukai, Ginther, Spaide, Bueno, and Himwich, 1967, 1970), while the human brain contains tryptamine and is capable of methylating it to DMT (Saavedra and Axelrod, 1972). More recently (Heller, Fischer, and Spatz, 1973) endogenous DMT has been detected in the rat brain. It is possible therefore that DMT is an endogenous psychotogen in schizophrenia, and even more likely that its presence predisposes schizophrenic subjects to a condition of DMT- (and DET-) tolerance.



Numerous animal studies with N,N-dialkyltryptamines have confirmed the results obtained in man. Thus, DMT and DET are typical hallucinogens in producing effects such as augmentation of the patellar reflex in cats (Cerletti, Taeschler, and Weidmann, 1968), head twitches in mice (Corne and Pickering, 1967), hyperthermia in rabbits (Brimblecombe, 1967; Cerletti and others, 1968), latency in the responses of rats trained to swim underwater (Uyeno, 1971), and disruption of conditioned avoidance responses in rodents (Smythies and others, 1967; Bradley and Johnston, 1970), and size discrimination responses in primates (Uyeno, 1969). Reliable quantitative information is rare in these animal studies, but DMT seems to be about three times as potent as mescaline in its effects on learned responses in primates and swimming latencies in

rats, but with only 0.006 or 0.1 of the potency of LSD in the two tests. The homologous series of *N,N*-dialkyltryptamines shows the same general trend of activity in the production of hyperthermia in rabbits or of behavioural changes in rats placed in the open field situation (Brimblecombe, 1967) and in the production of hallucinogenic syndromes in man (Szára and Hearst, 1962).

The cyclic analogue of DET, 3-(2-pyrrolidinoethyl)indole (4.13), was as active as the parent compound in behavioural tests in rodents, cats, and primates (Brimblecombe, 1967; Hunt and Brimblecombe, 1967; Bradley and Johnston, 1970). The compound was effective at doses down to 0.5 mg./kg. (s.c.) in disrupting the ability of monkeys to perform learned responses, but it is active only at levels which approach its lethal dose and it is unlikely to be tested in man.

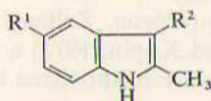


(4.15) R = H

(4.16) R = OCH₃

(4.17) R = NO₂

(4.18) R = CN



(4.19) R¹ = NH₂; R² = C₂H₅

(4.20) R¹ = NO₂; R² = C₂H₅

(4.21) R¹ = CH₂NH₂; R² = CH₃

In contrast, 1,4-*bis*-(2-indol-3-yl)piperazine (4.14) and its methoxy derivatives, which may be regarded as containing two fused DMT molecules, had no psychotomimetic properties in animals but rather a central depressant action (Brewster, Green, Pinder, and Thompson, 1973). Indene or benzo[*b*]thiophen isosteres of DMT or DET, in which the indolic imino moiety has been replaced by a methylene group or a sulphur atom respectively, are available (Winter, Gessner, and Godse, 1967; Campaigne, Neiss, Pfeiffer, and Beck, 1968) and are reported to be as active as the parent tryptamines as central stimulants. There is no information concerning their possible hallucinogenic action, but in view of the generalized decrease in tryptamine-like potency associated with changes in the indolic imino moiety (Taborsky, Delvigs, Palaic, and Bumpus, 1967; Pinder, Green, and Thompson, 1971) it is unlikely that they resemble DMT and DET.

Other structural variations of interest include gramine (4.15), which contains only a one-carbon side-chain and is without significant behavioural activity (Gessner, McIsaac, and Page, 1961; Ho, McIsaac, An, Harris, Walker, Kralik, and Airaksinen, 1970). The beneficial influence of aryl substitution in indolic compounds is illustrated by the moderate activities of the 5-methoxy (4.16),

5-nitro (4.17), and 5-cyano (4.18) derivatives in disrupting conditioned avoidance behaviour and swim-maze ability in rodents, though only at very high doses compared to the *N,N*-dialkyltryptamines. The compounds analogous to the gramines, but bearing the aminomethyl group in the 5-position together with 2,3-dialkyl substitution, were synthesized on the basis of the potent anti-serotonin actions *in vitro* of compounds like (4.19) and the reported hallucinogenic effects in animals of 5-nitro-3-ethyl-2-methylindole (4.20) (Shaw and Woolley, 1953; Woolley, 1960). Brimblecombe, Downing, and Hunt (1966) found such compounds to be relatively ineffective in open field or rabbit hyperthermia tests, though 5-aminomethyl-2,3-dimethylindole (4.21) was active in the former at doses down to 1 mg./kg. (s.c.).

3. *N,N*-DIALKYLTRYPTAMINES WITH ARYL SUBSTITUENTS

6-Hydroxylation

N,N-Dialkyltryptamines, as well as tryptamine (Jepson, Zaltzman, and Udenfriend, 1962; Lemberger, Axelrod, and Kopin, 1971) and melatonin (Taborsky, Delvigs, and Page, 1965), are metabolized by

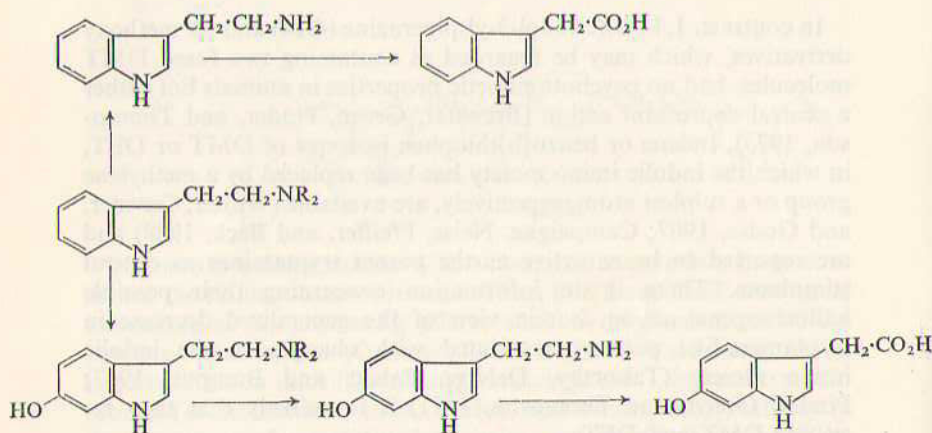


Fig. 4.1.—Principal metabolic pathways for *N,N*-dialkyltryptamines.

two main routes; dealkylation and oxidative deamination lead to indole-3-acetic acid, while 6-hydroxyindole-3-acetic acid is formed via 6-hydroxylation, conjugation, dealkylation, and oxidative deamination (Fig. 4.1). The isolation of the latter metabolite from

the urine of rats given DMT, together with an enzyme in rabbit liver which could hydroxylate and *N*-demethylate DMT (Szára and Axelrod, 1959), prompted Szára (1961a) to propose that 6-hydroxylation of *N*-alkylated tryptamines was an important step in the conversion of the parent molecule to a psychoactive metabolite or precursor thereof. Further evidence in support of this proposal was soon forthcoming: (a) liver microsomal systems could hydroxylate DMT, DET, and *N,N*-dipropyltryptamine, which are all hallucinogenic, but *N,N*-dibutyl- and *N,N*-diethyltryptamine were not 6-hydroxylated and are behaviourally inactive (Szára, 1964; Szára, and Hearst, 1962); (b) 6-hydroxydiethyltryptamine was more effective in disrupting the behaviour of rats, mice, and monkeys than was DET itself (Szára, Hearst, and Putney, 1962); (c) 6-fluorodiethyltryptamine was not hydroxylated and, while producing

Table 4.1.—RELATIVE POTENCIES OF DIMETHYLTRYPTAMINE (DMT) AND ITS 6-HYDROXY DERIVATIVE (6-OHDMT)

Drug	Man*	Rat 1†	Rat 2‡	Cat§	Monkey¶
DMT	1.0	1.0	1.0	1.0	1.0
6-OHDMT	<1.0	0.34	<0.5	<0.1	0.3–0.39

*Rosenberg and others, 1963. 6-OHDMT was inactive at the doses used (1 mg./kg., i.m.).

†Production of latency in the responses of rats trained to swim underwater (Uyeno, 1971).

‡Disruption of conditioned avoidance responses in rats; 6-OHDMT was inactive at 33 μ moles/kg. (i.p.) (Taborsky and others, 1967).

§Augmentation of patellar reflexes in cats; 6-OHDMT was inactive at 200 μ g./kg. (i.v.) (Cerletti and others, 1968).

¶Inhibition of size discrimination responses in monkeys (Uyeno, 1969).

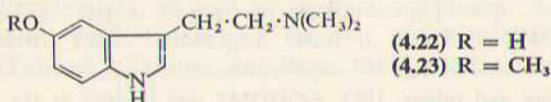
autonomic effects, had no apparent hallucinogenic actions in man (Kalir and Szára, 1963); (d) 5-chloro-, but not 6-chloro-, derivatives of α -methyl- and α -ethyl-tryptamine produced behavioural changes in animals (Whittle and Young, 1963); (e) the intensity of the hallucinogenic effect produced in man by DET paralleled the amount of the 6-hydroxy metabolite excreted in the urine (Szára, 1961a).

Nevertheless, while 6-hydroxylation is the major metabolic pathway for DMT and DET in the rat, it is only a minor route in man, where it accounts for only 4–7 per cent of administered drug (Elkes, 1962). Furthermore, 6-hydroxy-*N,N*-dimethyltryptamine is consistently less potent, and often inactive, when compared to the parent compound in both man and animals (Table 4.1). Indeed, in man there was little detectable difference between the compound

and a placebo (Rosenberg, Isbell, and Miner, 1963). A similar adverse effect upon potency in animal behavioural tests was evident with 6-hydroxylation of 5-methoxytryptamine (Taborsky and others, 1965) and its N,N-dimethyl derivative (Taborsky and others, 1967). Even Szára (1968, 1970) now seems convinced that 6-hydroxylation is not sufficient solely to account for the hallucinogenic actions of N,N-dialkyltryptamines but that other metabolic processes, possibly N-demethylation, may be more important. In this context, it is interesting that 6-hydroxytryptamine itself is taken up into brain tissue by serotonergic neurons (Lemberger and others, 1971), and it is possible that this may upset the normal function of serotonin in the central nervous system.

Bufotenin

The 5-hydroxy derivative of N,N-dimethyltryptamine, bufotenin (4.22) is, like the parent compound, a constituent of the hallucinogenic snuffs, prepared from various *Piptadenia* species (Holmstedt and Lindgren, 1967; Saxton, 1968a). The compound occurs widely



in higher plants and animals (Stowe, 1959), but its supposed presence in *Amanita muscaria* has now been disproved and the hallucinogenic properties of the mushroom are due to other constituents (see Chapter 7). The action of bufotenin as a hallucinogen is still the source of some dispute. Fabing and Hawkins (1956) reported that intravenous injection over 3 minutes of 8–16 mg. of bufotenin to human volunteers produced primary visual disturbances, alteration of time and space perception, and paraesthesia, although illusions and visual hallucinations were rare. Perhaps some of the confusion arises from the continual and erroneous assertions (see, for examples, Downing, 1964; Hofmann, 1968; Burger, 1970; Brown, 1972) that Fabing and Hawkins used doses of 2–16 mg./kg. in their experiments and not total doses of 2–16 mg.; at the former rate the dose would have been over 1 g. of bufotenin intravenously! Nevertheless, other investigators found no subjective or objective changes in volunteers given intravenous doses of up to 20 mg., in contrast to the prominent hallucinogenic effects of DMT in the same trials (Turner and Merlis, 1959), while oral administration of up to 100 mg. of the drug were also without effect; even snuffing of similar doses failed to produce the expected response (Hofmann, 1963a, b; Holmstedt and Lindgren, 1967). However, bufotenin has pronounced autonomic

activity, it is found in the urine of acute schizophrenics, and its administration to chronic schizophrenics given monoamine oxidase inhibitors reactivates their acute psychosis. It may play a role in schizophrenia as a result of excessive N-methylation of 5-hydroxytryptamine (Saavedra and Udabe, 1970; Saavedra and Axelrod, 1972).

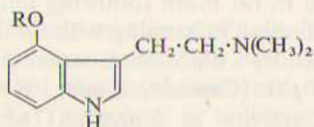
Animal studies with bufotenin are equally equivocal to those in man. It appears to inhibit rather than augment patellar reflexes in cats (Cerletti and others, 1968), has only one-fifth of the activity of DMT in producing head twitches in mice (Corne and Pickering, 1967), and is very weakly active in affecting conditioned avoidance responses and swimming ability in rodents (Gessner and others, 1961; Gessner and Page, 1962; Taborsky and others, 1967; Ho and others, 1970). The drug appears to attenuate locomotor activity in animals ranging from rats to primates (Evarts, 1956; Winocur, Bagchi, and Young, 1969), and the general consensus of opinion (Maire and Hixon, 1966; Winocur, Bagchi, and Hubbard, 1971) is that bufotenin reduces an animal's responsiveness to external stimuli. The relative lack of central effects of bufotenin may be due to its inability to enter the central nervous system. Many of its effects, but not those of DMT, are blocked by xylamidine, an agent which selectively antagonizes the peripheral component of the actions of tryptamine-like agents (Winter, 1972). Furthermore, only very small amounts of bufotenin are found in rat brain following intravenous administration (Vogel, 1969), a finding in keeping with the low lipid solubility of the drug as measured by a chloroform-water coefficient of only 0.06 at physiological pH (Gessner, Godse, Krull, and McMullan, 1968). The weak activity at 5 mg./kg. (s.c.) of 5-hydroxy-N,N-diethyltryptamine in the open field test with rats may well be due to a similar lack of lipid solubility and consequent poor entry into the brain (Hunt and Brimblecombe, 1967). 5-Acetoxy-N,N-dimethyltryptamine may be worthy of a clinical trial as a lipid-soluble derivative of bufotenin, since the compound is very effective in disrupting conditioned avoidance responses in rodents (Gessner and others, 1968; Gessner, 1970).

The activity of the South American hallucinogenic snuffs may well reside chiefly in their content of the 5-methyl ether of bufotenin, 5-methoxy-N,N-dimethyltryptamine (5-MeODMT, 4.23), which is not only the major constituent in many cases (Holmstedt and Lindgren, 1967; Saxton, 1968a; Lai, Tin-Wa, Mika, Persinos, and Farnsworth, 1973) but is also the most potent in many behavioural tests. It is about three times as potent as DMT in its effect on conditioned avoidance responses and swim-maze ability in rodents (Gessner and others, 1961; Gessner and Page, 1962; Smythies and others, 1967; Ho and others, 1970), and is almost as potent as LSD

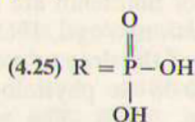
in producing a violent and rapid sham-rage response in cats (Benington, Morin, and Clark, 1965). The 5-methoxy derivative of DET, a synthetic compound, has about the same activity in its effects on conditioned avoidance responses, producing a failure rate of 30 per cent in rodents after doses of 10 μ moles/kg. (i.p.) (Gessner and others, 1968; Gessner, 1970). The high potency of these compounds may be due to their high lipid solubilities; thus, 5-MeODMT and its diethyl analogue have chloroform-water partition coefficients at physiological pHs of 3.30 and 7.89 respectively, compared to the 1.85 of DET itself. Both of these lipophilic derivatives of bufotenin will undoubtedly prove to be hallucinogenic when administered to man; indeed, preliminary reports (Shulgin, 1970) indicate that 5-MeODMT has a potency between those of psilocin and LSD, with an effective dose of 5–10 mg. (i.p.) but being inactive by oral administration.

Psilocin and Psilocybin

The active principles of *teonanacatl*, the sacred mushroom of Central America, are the alkaloids psilocin (4.24) and psilocybin (4.25), which are respectively 4-hydroxy-N,N-dimethyltryptamine and



(4.24) R = H



(4.26) R = CH₃

its phosphoryl derivative. Most species of *Psilocybe* and a number of *Stropharia* and *Conocybe* species contain these compounds, which are derived biosynthetically both by 4-hydroxylation of DMT and by N-methylation of 4-hydroxytryptamine (Leung and Paul, 1968). Psilocybin forms about 0.2–0.4 per cent of the dried mushrooms, which contain only trace amounts of psilocin. This may be a consequence of the sensitivity of the latter to oxidation and to its relatively poor water solubility, but it, and phosphoric acid, are obtained when psilocybin is hydrolyzed. The two compounds are representative of the very few indoles which occur naturally with a 4-substituent, all others except the *Mitragyna* alkaloids bearing hydroxyl groups in the 5-, 6-, or 7-positions.

Psilocin and psilocybin produce hallucinogenic effects in man that are similar to those produced by LSD or mescaline, the medium oral dose of 4–8 mg. being equivalent to the consumption of about

2 g. of dried *Psilocybe mexicana* (Heim, Hofmann, Brack, and Cailleux, 1958). A large number of carefully controlled studies have confirmed this opinion (Delay, Pichot, Lempérière, and Nicolas-Charles, 1958; Delay, Pichot, Lempérière, Nicolas-Charles, and Quélin, 1959; Gnirss, 1959; Rümmele, 1959; Malitz, Escover, Wilkins, and Hoch, 1960; Heimann, 1961, 1962; Hollister, 1961; Rümmele and Gnirss, 1961; Wolbach, Miner, and Isbell, 1962; Leary, Litwin, Metzner, and Metzner, 1963; Hollister and Sjöberg, 1964); they suggest that the time-courses of the reactions are shorter than, though qualitatively identical to, those of LSD or mescaline. Psilocin is claimed to be about 1.4 times as potent as psilocybin, but they are equipotent on a *molar* basis. Cross-tolerance exists between LSD and psilocybin, indicating that they probably act via a common mechanism or pathway (Isbell, 1959; Isbell, Wolbach, Wikler, and Miner, 1961). Certainly, patients receiving LSD for psychotherapy were apparently unable to realize the change when psilocybin was substituted, and the natural indole has often replaced LSD in such treatment (Leuner, 1968).

Oral doses of a few milligrams of either of the *Psilocybe* alkaloids produce, within 20–30 minutes, effects on mood and environmental contact in that there is frequently a pleasant sensation of intellectual and bodily relaxation and detachment. This may be accompanied by a feeling of extraordinary lightness, a loss of corporeity. Psychic changes are more profound with higher doses and consist of changes in spatial and temporal perception, visual hypersensitivity, and illusions and hallucinations. Individual responses are very sensitive to the influence of mood and expectation, and long-forgotten childhood memories can often be recalled. The drugs are claimed to suspend or temporarily deactivate the cognitive-perceptual screening structures of the brain (Metzner, Litwin, and Weil, 1965).

Psilocin and psilocybin are active in the usual behavioural tests in animals. Thus, they augment the patellar reflex in cats (Cerletti and others, 1968), disrupt conditioned avoidance responses in rodents (Gessner and others, 1968), and are about 2–3 times more potent than DMT in producing head twitches in mice (Corne and Pickering, 1967). Psilocybin is equipotent with DOM and about one-twentieth as potent as LSD in disrupting swimming ability in rodents (Uyeno, 1971) and learned size-discrimination responses in squirrel monkeys (Uyeno, 1969). The therapeutic index for psilocin and psilocybin is very high, since they are less than half as toxic to mice as is mescaline but with at least 50 times its behavioural activity (Hofmann, 1960).

In contrast to the pronounced enhancement of hallucinogenic activity associated with methylation of the 5-hydroxy group of

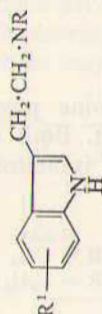
bufotenin, 4-methoxy-N,N-dimethyltryptamine (4.26) is less potent than psilocybin. The respective ED_{50} values (μ moles/kg., i.p.) for disrupting size-discrimination performance in monkeys and swimming ability in rodents are 18.9 and 2.9 (Uyeno, 1969) and 20.1 and 8.7 (Uyeno, 1971). Perhaps these results reflect the differing lipid solubilities of the compounds, because bufotenin, 5-MeODMT, psilocin, and compound 4.26 have respective chloroform-water partition coefficients of 0.06, 3.30, 5.52, and 2.28 (Gessner and others, 1968). Clearly, little advantage in physico-chemical characteristics is gained by methylation of the 4-hydroxy group of psilocin compared to the 5-hydroxy group of bufotenin. Nevertheless, psilocin is more lipid soluble at physiological pH than is psilocybin, and the phosphoric acid radical of the latter serves merely as a protecting group which is hydrolytically removed prior to entry of the free psilocin molecule into the brain. The similarity of the pharmacological profiles of the two compounds coupled with demonstration of the *in vivo* dephosphorylation of psilocybin make it likely that the central effects of psilocybin are exerted only after its conversion into psilocin (Horita and Weber, 1962; Horita, 1963). Thus, administration of psilocybin to intact mice results in the accumulation of high concentrations of psilocin in the kidney and liver within 10–20 minutes and in the brain within 25–30 minutes, a distribution pattern identical to that observed following administration of psilocin itself (Kalberer, Kreis, and Rutschmann, 1962; Hopf and Eckert, 1969). Behavioural effects closely followed the time-course of increases in brain levels of psilocin in each case.

Psilocin is rapidly absorbed to the extent of about 50 per cent from the gastrointestinal tract, and it, and its metabolites, are excreted mainly in the urine. Most of the products, 65 per cent in the urine and 15–20 per cent in the bile and faeces, are excreted in the first 8 hours, but at least 10–20 per cent is retained longer so that even after 7 days significant quantities of metabolites are found in the urine (Gessner, Khairallah, McIsaac, and Page, 1960; Kalberer and others, 1962). The dimethylaminoethyl side-chain is particularly resistant to metabolic transformation, and oxidative deamination plays a very minor role to the extent of less than 4 per cent in the metabolism of psilocin. At least 25 per cent of the administered drug is excreted unchanged, the main metabolic products being various conjugates of the 4-hydroxy group.

Miscellaneous Tryptamines

Structure-activity relationships in the tryptamines are based mainly on the augmentation of patellar reflexes in cats (Cerletti and others,

Table 4.2.—BEHAVIOURAL ACTIVITIES OF SOME TRYPTAMINES



R	R'	Effective Dose in Man (mg.)	ED ₅₀ (Monkeys) Size-discrimination (μmoles/kg., i.p.)	ED ₅₀ , Swimming Latency (Rats) (μmoles/kg., i.p.)	Percentage Failure Rate, Conditioned Avoidance (Rats) (10 μmoles/kg., i.p.)	Minimum Effective Dose, Open Field (Rats) (mg./kg., s.c.)
(CH ₃) ₂	H	70 (i.m.)	25.5	20.1	—	2
(C ₂ H ₅) ₂	H	70 (i.m.)	—	—	4.7	2
(CH ₃) ₂	5-OH	16 (i.v.) (?)	—	—	—	15
(CH ₃) ₂	4-OH	4.8 (p.o.)	2.9*	8.7*	6.0	—
(CH ₃) ₂	5-OCH ₃	5 (i.m.)	—	—	29.3	—
(CH ₃) ₂	4-OCH ₃	?	18.5	22.0	25.6	—
(CH ₃) ₂	5-O-COCH ₃	?	—	—	41.0†	—
CH ₃ , C ₂ H ₅	5-OCH ₃	?	—	—	76.6	—
	?	?	—	—	—	0.1

* As its phosphoryl derivative (psilocybin).

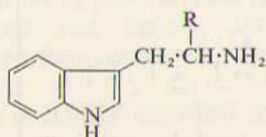
† This high potency is a reflection of *in vivo* hydrolysis to bufotenin.



1968). Optimum potency is associated with a dimethylaminoethyl side-chain at position 3, a 4-hydroxy group, and an unsubstituted indolic imino group. Thus, psilocin is the most potent of a series of 4-hydroxytryptamines, replacement of the 4-hydroxy group by other substituents or its removal to the 5-, 6-, or 7-positions is deleterious, and 1-alkylation abolishes activity. Compounds of interest which have not been tested in man include 5-methoxy-N-ethyl-N-methyltryptamine, which is more potent than the N,N-dimethyl analogue in behavioural tests in rodents (Gessner and others, 1968), and 5-methoxy-3-(2-pyrrolidinoethyl)indole, which is the most potent tryptamine so far revealed by the open field test, though its high toxicity will preclude tests in man (Brimblecombe, 1967; Hunt and Brimblecombe, 1967). Even with these compounds, removal of the methoxy group to other positions reduces activity as does demethylation to the bufotenin analogues. Table 4.2 collects details of the tryptamines studied extensively in man as well as those, so far untested in man, which seem very potent in animals.

4. α -ALKYLTRYPTAMINES

α -Alkylation, like N,N-dialkylation, of tryptamine prevents the action of monoamine oxidase to a large extent. Both α -methyl- (4.27) and α -ethyltryptamine (4.28) are potent inhibitors of the



(4.27) R = CH₃

(4.28) R = C₂H₅

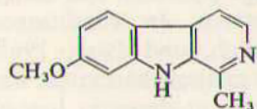
enzyme, and the latter compound has been marketed as an anti-depressant drug under the name of etryptamine or Monase (Hoffer and Osmond, 1967). In view of the increase in brain serotonin levels associated with the action of these drugs and with that of many hallucinogens (see Chapter 8), it is not surprising that hallucinogenic reactions have been reported with the α -alkyltryptamines. α -Methyltryptamine produced a subjective LSD-like reaction in man, a dose of 20 mg. being equivalent to 50 μ g. of LSD with effects appearing only after 3-4 hours following oral administration (Murphree, Jenney, and Pfeiffer, 1960). The majority of subjects in a larger study (Murphree, Dippy, Jenney, and Pfeiffer, 1961) reported that they were nervous, irritable, restless, and could not relax. Visual effects were not prominent and the experience was likened to an unpleasant, long-lasting LSD reaction. α -Ethyltryptamine produced occasional visual disturbances, lethargy,

sedation, and slight euphoria in oral doses of 150 mg., and it is clearly less potent than the methyl analogue. Szára (1961a) reported that 20 mg. of α -methyltryptamine was equivalent to 60 mg. of DET in psychotomimetic activity with more perceptual distortions and less autonomic activity. Neither of the α -alkyltryptamines is particularly potent in behavioural studies in animals (Hoffer and Osmond, 1967) and their hallucinogenic potential is clearly limited in comparison to other tryptamines. In production of head twitches in mice, for example, α -ethyltryptamine was inactive while α -methyltryptamine was only slightly more active than mescaline with an ED_{50} of 7.9 mg./kg. (s.c.) (Corne and Pickering, 1967).

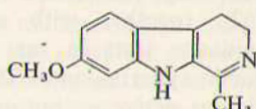
II. β -CARBOLINES

1. HARMALA ALKALOIDS

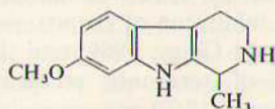
The harmala alkaloids are the biologically active constituents of various *Banisteriopsis* species from which are made the magic beverages, such as caapi and ayahuasca, of the South American Indians



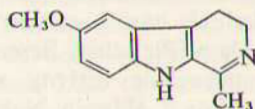
(4.29)



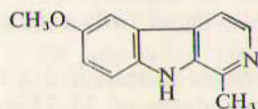
(4.30)



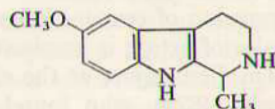
(4.31)



(4.32)



(4.33)



(4.34)

(Rivier and Lindgren, 1972) (see Chapter 1). Harmine (4.29) is the major alkaloid, and harmaline (4.30) and (+)-1,2,3,4-tetrahydroharmine (4.31) the minor alkaloids, in these plants, and they are representatives of the class of indole derivatives known as β -carbolines. They also occur widely throughout the world in other species (Deulofeu, 1967), but of these only *Peganum harmala* has a

history of use as an intoxicant (Naranjo, 1967). Nevertheless, they are the minor alkaloids in *Virola* species, from which are made hallucinogenic snuffs such as Yakee, Paricá, and Epená, and whose major alkaloids are various tryptamines (Agurell, Holmstedt, Lindgren, and Schultes, 1968, 1969; Cassady, Blair, Raffaui, and Tyler, 1971). It is probable that such compounds as 6-methoxyharmalan (4.32), 6-methoxyharman (4.33), and 6-methoxytetrahydroharman (4.34) potentiate the central actions of these tryptamines by their inhibition of monoamine oxidase.

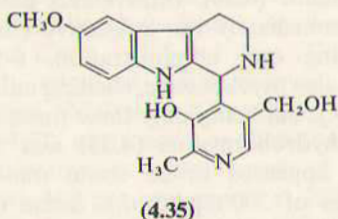
There is little doubt that caapi and ayahuasca are hallucinogenic in man (Hoffer and Osmond, 1967; Rivier and Lindgren, 1972), but there is considerable scepticism about the central effects in man or animals of the pure alkaloids. Large doses of harmine and its congeners, like many indolealkylamines, are tremorogenic in most species (Brimblecombe and Pinder, 1972); doses of 10–20 mg./kg. (i.p.) of harmine, for example, produce rest tremors of frequency 14–16 Hz in mice. Toxic doses produce respiratory arrest with falls in temperature and blood-pressure, the latter being due to a weakening of cardiac muscle. Smaller doses lead to restlessness and anxiety in monkeys (Chen and Chen, 1939) and dogs (Gershon and Lang, 1962), together with apparent hallucinations. In conditioned avoidance tests in rats (McIsaac, Khairallah, and Page, 1961) 6-methoxyharmalan (4.32), also known as 10-methoxyharmalan, was twice as active as bufotenin. It caused errors at doses as low as 8 μ moles/kg. (i.p.) with 100 per cent errors at 250 μ moles/kg.; the isomeric harmaline was less active. The central effects of harmala alkaloids have been correlated with their inhibition of monoamine oxidase (Pletscher, Besendorf, Bächtold, and Geigy, 1959) and the tremorogenic activity with occupation of serotonin receptors (Battista, Goldstein, Nakatani, and Anagnoste, 1969) or suppression of dopaminergic neuronal activity (Poirier, Singh, and Boucher, 1968), but recent studies on harmaline-induced hypothermia and depression of operant behaviour suggest that none of these possible modes of action is involved (Winter, 1971).

The first report of the effects of pure harmine in man is due to Lewin (1928), who found that subcutaneous doses of 25–75 mg. produced euphoria. Later workers (Turner, Merlis, and Carl, 1955) doubted whether this should be regarded as a hallucinogenic reaction. Pennes and Hoch (1957) found that mental patients responded to intravenous doses of 150–200 mg. with an LSD-like reaction, but oral administration of up to 960 mg. had only minimal effects on perception. The reaction resembled a cyclical confused state with intermittent drowsiness and sleep; perceptual disturbances were frequent and visual hallucinations occurred with the eyes closed.

Subjects also noted some vertigo, lightheadedness, ataxia, and impairment of speech, and the effects disappeared within 24 hours. The experience was not pleasant in contrast to that usually seen with LSD or with mescaline, but Hoffer and Osmond (1967) have pertinently criticized the setting of the experiments as being uncondusive to the more desirable aspects of the hallucinogenic experience. Harmine, LSD, and mescaline are reported to produce essentially similar reactions in both normal and psychotic patients (Vargas, 1959). Nevertheless, the apparent superiority of extracts of *Banisteriopsis* over the pure harmine prompted the suggestion (Hochstein and Paradies, 1957) that either harmaline or 1,2,3,4-tetrahydroharmine, or other as then unidentified constituents, were the psychoactive compounds. Naranjo (1967) has now confirmed their hallucinogenic activity in man together with that of 6-methoxyharmalan and 6-methoxytetrahydroharman.

6-Methoxyharmalan (4.32) produces marked subjective changes in man at oral doses of 1.5 mg./kg., being about 1.5 times as active as the isomeric harmaline (4.30). Intravenous doses of 1 mg./kg. are effective almost immediately but subjective changes appear about one hour following oral administration. 6-Methoxytetrahydroharman (4.34) was also psychoactive, eliciting mild subjective changes at 1.5 mg./kg. (p.o.), but being only three times as potent as harmaline. 1,2,3,4-Tetrahydroharmaline (4.31) was tested in only one subject, where it appeared to be about one-third as potent as harmaline in doses of 300 mg. (p.o.). Some of the responses to harmala alkaloids reported by Naranjo are nausea, dizziness, and general malaise, together with paraesthesias of the hands, feet, and face, followed by numbness. Distortions of body image and of objects in the environment, so common with LSD or mescaline, were not present and there was no enhancement of colour. However, there was abundant closed-eye imagery, hypersensitive hearing, and the superposition of imaginary scenes simultaneously with an undistorted perception of surrounding objects. Naranjo suggests that the inspiration and heightened introspection induced by the drugs, which involves subjects 'seeing' scenes in a different time and place, are exactly what the South American Indians experience following the consumption of ayahuasca or caapi. Harmaline and its congeners may stimulate the midbrain reticular formation in man as they do in cats, leading to such phenomena as double contours and persistence of after-images. The neurophysiological picture apparently matches the 'dreaming' state of the Indian, with lethargy, immobility, closed eyes, and generalized withdrawal from the environment, together with an alertness to mental processes and an activation of fantasy (Naranjo, 1967).

Harmin is rapidly absorbed and metabolized in man following intravenous injection, as a consequence of its high lipid solubility and ability to cross biological membranes (Slotkin, DiStefano, and Au, 1970). In both man and the rat, harmol, the *O*-demethylated derivative of harmine, and its sulphate and glucuronide conjugates are the major metabolites, while 4 hours after administration of 0.5 mg./kg. (i.v.) to man less than 1 per cent of free harmine was detectable in the blood. Of more direct interest to the mode of action of harmine and other β -carbolines than their metabolism is their possible formation *in vivo* from various indole-3-alkylamines (Airaksinen and McIsaac, 1968). This hypothesis was originally proposed by McIsaac (1961a) as a biochemical basis for mental disease, and is an attractive alternative to the adrenochrome hypothesis (Hoffer and Osmond, 1967; see Chapter 3) or the possible production of endogenous N,N -dialkyltryptamines (Saavedra and Axelrod, 1972; see I,2). Certainly, adrenoglomerulotropine, a



hormone of the pineal body, is identical with 6-methoxytetrahydroharman and is formed both *in vivo* and *in vitro* by condensation of 5-methoxytryptamine with acetaldehyde (Farrell and McIsaac, 1961; McIsaac, 1961b). It is possible also that 6-methoxyharmalan could be derived from melatonin by dehydrative cyclization, and the compound has been tentatively proposed as a melatonin metabolite (McIsaac and others, 1961). Both β -carbolines are hallucinogenic in man (Naranjo, 1967), while several others that could possibly be derived from aldehyde condensation of tryptamines show behavioural effects in animals (Taborsky and McIsaac, 1964b). The product (4.35) of condensation between 5-methoxytryptamine and pyridoxal, for example, is very toxic to rodents and produces a long-term state of behavioural aberration following a single injection (i.p.) of 13.6–41.3 μ moles/kg. It is therefore possible that β -carbolines play a role in mental illness as endogenous psychotogens, particularly since their formation will inhibit biodegradation of the tryptamine precursors by monoamine oxidase and thereby

increase their own synthesis (Fig. 4.2). Certainly, this may be the basis for the hallucinogenic properties of ayahuasca and its relatives, since they contain considerable amounts of various tryptamines as well as the more familiar harmala alkaloids (Rivier and Lindgren, 1972).

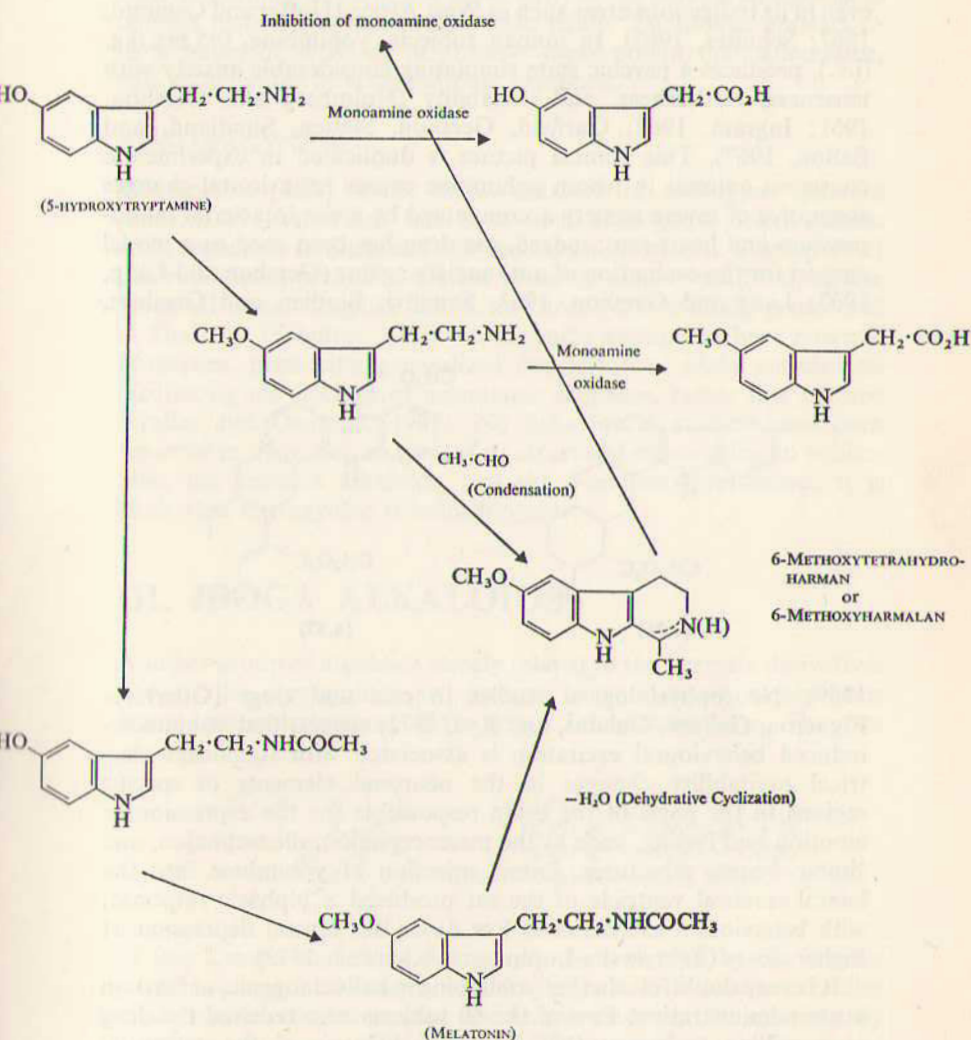
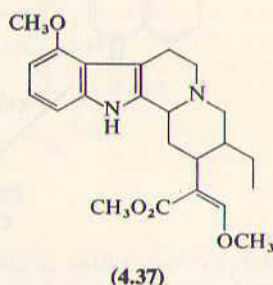
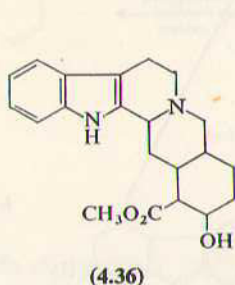


Fig. 4.2.—Scheme of the possible formation *in vivo* of hallucinogenic β -carbolines from endogenous tryptamines.

2. YOHIMBINE

Yohimbine (4.36) occurs in such a widespread variety of plants, particularly in the rubiaceous genera *Pseudocinchona* and *Yohimbe* (Monteiro, 1969), that it is almost inevitable that its effects as a crude drug have been known to man for many centuries. Nevertheless, the drug does not seem to enjoy a reputation as an intoxicant even in its indigenous areas such as West Africa (Hoffer and Osmond, 1967; Schultes, 1967). In human subjects, yohimbine, 0.5 mg./kg. (i.v.), produces a psychic state simulating considerable anxiety with tenseness, restlessness, and irritability (Holmberg and Gershon, 1961; Ingram, 1962; Garfield, Gershon, Sletten, Sundland, and Ballou, 1967). This clinical picture is duplicated in experimental conscious animals in whom yohimbine causes behavioural changes suggestive of severe anxiety accompanied by a rise in arterial blood-pressure and heart-rate; indeed, the drug has been used as a model agonist for the evaluation of anti-anxiety agents (Gershon and Lang, 1962; Lang and Gershon, 1963; Sanghvi, Bindler, and Gershon,



1969). Neurophysiological studies in cats and dogs (Guerrero-Figueroa, Gallant, Galatas, and Rye, 1972) suggest that yohimbine-induced behavioural excitation is associated with significant electrical excitability changes in the neuronal elements of specific regions in the parts of the brain responsible for the expression of emotion and feeling, such as the mesencephalon, diencephalon, and limbic system structures. Direct injection of yohimbine into the lateral cerebral ventricle of the rat produced a biphasic response, with behavioural excitation at low doses but central depression at higher doses (Zebrowska-Lupina and Kleinrok, 1973).

It is very doubtful whether yohimbine is hallucinogenic, at least on acute administration. Few of the 60 subjects who received the drug were willing to repeat the experience because of the extremely unpleasant nature of the anxiety syndrome (Holmberg and Gershon,

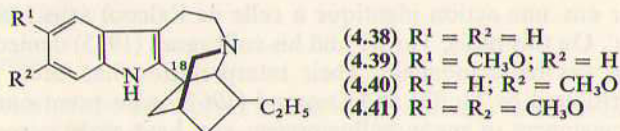
1961). Chronic administration of the alkaloid in thrice-weekly doses of 20–40 mg. (i.m.) to schizophrenic patients produced gross behavioural disturbances one hour after injection in 3 of 5 cases. Visual and auditory hallucinations were prominent, to be replaced within a few hours by euphoria and alertness. Pretreatment with barbiturates or librium reduced the anxiety but similar treatment with imipramine so increased the severity of the psychic changes as to convert restlessness and anxiety into panic. Yohimbine appears to be a powerful activator of anxiety, more potent than adrenaline, and an activator of schizophrenic psychosis.

3. MITRAGYNINE

Mitragynine (4.37) is the major alkaloid of *Mitragyna speciosa* (Saxton, 1968b), which has been used throughout south-eastern Asia, especially in Siam and Borneo, as an intoxicant. The leaves of this rubiaceous plant are chewed alone or mixed with betel, or else prepared for smoking like opium, and its use is now legally proscribed in Thailand (Schultes, 1967). Mitragynine appears to have narcotic properties, producing generalized depression of plain muscle and facilitating the passage of autonomic impulses, rather like cocaine (Hoffer and Osmond, 1967). No behavioural studies have been reported in man, but, in view of its structural relationship to yohimbine, the harmala alkaloids, and the 4-methoxytryptamines, it is likely that mitragynine is hallucinogenic.

III. IBOGA ALKALOIDS

Another group of alkaloids closely related to the harmala derivatives and to the tryptamines are present in various apocynanaceous plants, particularly those of the genus *Tabernanthe iboga*. The root

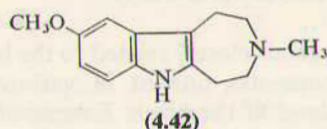


of this Central and West African shrub is chewed by the natives to offset hunger and fatigue, while in larger doses it produces excitement, mental confusion, and a drunken madness characterized by prophetic utterances (Tyler, 1966). There are few ethnobotanical references to its use as a vision-inducing narcotic although it has

long held an established place in African folk medicine, but Schultes (1969) records that it is used for this purpose in the ceremonies of the Bwiti cult in Gabon. *Tabernanthe iboga* contains some 12 alkaloids of which the biologically significant appear to be ibogamine (4.38), ibogaine (4.39), tabernanthine (4.40), and ibogaline (4.41); the related *Voacanga* alkaloids, which bear a carbomethoxy substituent at C-18, are of little pharmacological interest (Taylor, 1969).

The observations of early workers on the effects of ibogaine on spontaneous behaviour in animals (Lambert and Heckel, 1901; Phisalix, 1901; Lambert, 1902) have been confirmed by modern pharmacologists (Schneider and Sigg, 1957; Zetler and Unna, 1959; Gershon and Lang, 1962). Thus, intravenous doses of 2–10 mg./kg., or twice this subcutaneously, of ibogaine hydrochloride produce immediate effects in cats and dogs consisting of tremor, excitation, and rage, together with fear and escape reactions. The symptomatology is suggestive of hallucinations, maximal excitement being reached within 10–20 minutes and disappearing after 1–2 hours. Ibogaine has a cocaine-like narcotic effect in animals (Pouchet and Chevalier, 1905) and man (Steinmetz, 1961), which may explain the ethnopharmacological analogy between *Tabernanthe iboga* in West Africa and *Erythroxylum coca* in South America. Nevertheless, there is considerable doubt as to whether the alkaloids of *Tabernanthe iboga* are hallucinogenic.

The original report of the effects of pure ibogaine in man is due to Dybowski and Landrin (1901), who suggested that it was a stimulant which did not disturb the thought processes of the user: 'Ibogaine



avait sur eux une action identique a celle de l'alcool sans troubler la raison'. On this basis, Turner and his colleagues (1955) denied that ibogaine was hallucinogenic. Their interpretation has been pertinently criticized by Hoffer and Osmond (1967), who point out that native consumers of many hallucinogens can have vivid *perceptual* changes with but little disturbance of thought, a dichotomy also seen when unsophisticated subjects eventually become experienced with the drugs. Certainly, Naranjo (1967) reports that ibogaine is a true hallucinogen, although he gives no details of doses, routes of administration, or symptomatology, and he has claimed a patent use for the alkaloid in a psychopharmaceutical preparation which

also contains the hallucinogen 3,4-methylenedioxyamphetamine (Bocher and Naranjo, 1969). Ibogaine has been placed in the same category as LSD and other hallucinogens by the U.S. Food and Drug Administration (Farnsworth, 1968).

There appear to be no detailed reports in the literature regarding the psychic effects of ibogaine in man, and the only iboga alkaloid to be so studied is the related ibogaline (Schmid, 1967). Oral doses of 0.1–1.2 mg./kg. of ibogaline hydrochloride produced a state of intoxication and mild sedation without any pronounced productive symptomatology and in the absence of profound changes in mental state usually associated with hallucinogenic drugs. In only 5 of 12 subjects were psychic changes observed, with visual hallucinations and changes in perception of a relatively minor nature. The contrast between this report and the cultic use of *Tabernanthe iboga* suggests that one of the other alkaloidal constituents of the plant may be the active hallucinogen or that the doses of 10–105 mg. used by Schmid are inadequate. *Tabernanthe iboga* can contain up to 6 per cent of iboga alkaloids and it is clear that the West African native can ingest very high oral doses of these compounds if the root is chewed for a sufficiently long time.

The iboga alkaloids are long overdue for a detailed examination of their psychic effects in man. It is interesting that simplification of the iboga structure to give the hexahydroazepino[4,5-b]indoles (for example, 4.42) enhances the tryptamine-like properties, at least as far as tremorogenic activity is concerned, but also enhances the sedative effects. Thus, these compounds have chlorpromazine-like properties in both man and animals (Hester, Tang, Keasling, and Veldkamp, 1968).

IV. LYSERGIC ACID DERIVATIVES

1. OLOLIUQUI

Constitution

The history of the Mexican magical drug ololiuqui is bedevilled by controversy (Hoffer and Osmond, 1967). Though correctly placed in the *Convolvulaceae* as early as 1854 and identified as *Rivea corymbosa* in 1897, the erroneous but dogmatic view of Safford (1915) that ololiuqui was a species of *Datura* prevailed for no better reason than that 'it is not known that any of the *Convolvulaceae* are narcotic, though many of the *Solanaceae* are'. Schultes (1941) finally settled the botanical issue, but doubts were revived by the inability of

Kinross-Wright (1959) to repeat the self-experiments of Osmond (1955) with the seeds of *Rivea corymbosa*. Hofmann's subsequent isolation from ololiuqui of derivatives of lysergic acid (Hofmann and Tschertter, 1960), previously found only in fungi, was met with a state of disbelief bordering on accusations of scientific fraud. Nevertheless, it is now accepted that both *Rivea corymbosa* and *Ipomoea*

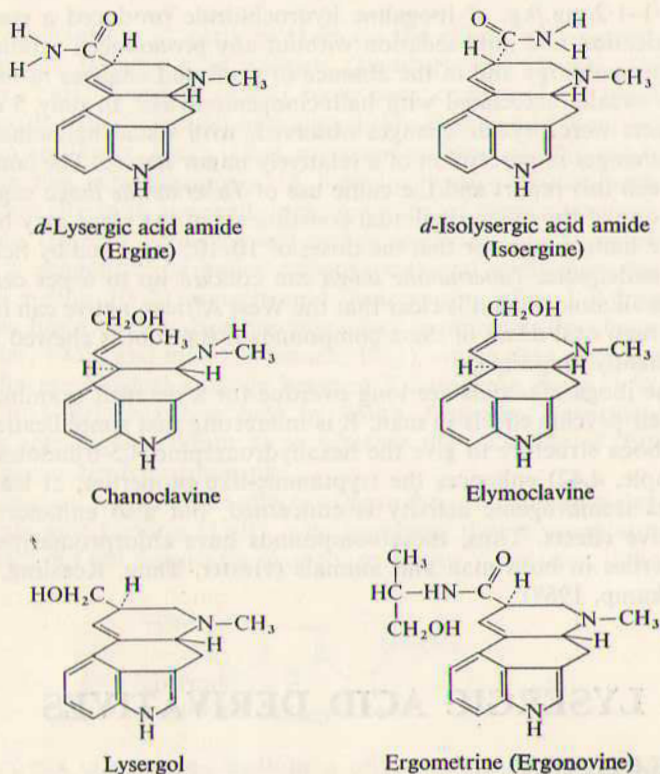


Fig. 4.3.—Derivatives of lysergic acid found in *Rivea corymbosa* (ololiuqui) and *Ipomoea violacea* (badoh negro).

violaceae, from which are prepared the magical drugs ololiuqui and badoh negro respectively, contain a number of indoles related to the ergot alkaloids (Fig. 4.3).

d-Lysergic acid amide (ergine) is the major constituent of the seeds of both *Rivea corymbosa* and *Ipomoea violacea*, together with smaller amounts of *d*-isolysergic acid amide (isoergine), chanoclavine, elymoclavine, and the *N*-(1-hydroxyethyl)amides of lysergic and

isolysergic acids. Lysergol is found in *Rivea* but not in *Ipomoea*, while ergometrine (ergonovine) is present in the latter but not the former (Hofmann and Tschertter, 1960; Hofmann, 1961b, 1964; Hofmann and Cerletti, 1961; Gröger, 1963). The alkaloids are present in the embryo but not in the seed coat of these species and have not arisen by fungal contamination (Taber and Heacock, 1962), but they are also found in some vegetative tissues such as the leaves and stems (Taber, Heacock, and Mahon, 1963; Taber, Vining, and Heacock, 1963). The total alkaloid content of *Rivea* seeds is about 0.012 per cent, rather less than that (0.06 per cent) in *Ipomoea*, which may explain the reputedly greater potency of badoh negro over that of ololiuqui. The constituents of these convolvulaceous plants were not new even in 1960; the isomeric lysergic acid amides had previously been obtained as cleavage products by hydrolysis of the ergot alkaloids (Smith and Timmis, 1932, 1936), while chanoclavine (Hofmann, Brunner, Kobel, and Brack, 1957) and elymoclavine (Abe, Yamano, Kozu, and Kusumoto, 1955) had been isolated from ergot. Lysergol, ergometrine, and the isomeric amides had also been synthesized in the laboratories of the Sandoz group (Stoll, Hofmann, and Schlienz, 1949).

Pharmacology

The first carefully controlled experiments with ololiuqui were those of Osmond (1955). Self-administration of 60–100 *Rivea* seeds (about 1 mg. of total alkaloid), which were pulverized and washed down with water, produced anergia and irritable apathy combined with a degree of heightened visual perception and an increase in hypnagogic phenomena, eventually leading after about 4 hours to feelings of calm, alertness, and relaxed well-being. Effects appeared rapidly (within 20 minutes) but were of short duration and left no hangover. Kinross-Wright (1959) was unable to reproduce these results in volunteers, possibly because of inadequate preparation of the ololiuqui seeds with subsequent poor absorption of the active alkaloids. Nevertheless, two recent studies in former opiate addicts (Isbell and Gorodetzky, 1966) and normal subjects (Heim, Heimann, and Lukacs, 1968) suggest that ololiuqui is not a true hallucinogen even in doses as high as 5 mg. of total alkaloids and does not produce the typical alterations in perception and consciousness associated with mescaline and LSD. Drowsiness, apathy, and mental detachment seem to be the major effects of either crude extracts of ololiuqui or of synthetic alkaloid mixtures, both of which contain a strong sedative component in their central actions. Heim and his colleagues concluded that the heavy intoxication with

reduced consciousness and autonomic side-effects produced by large doses of ololiuqui was similar to that encountered in toxic psychoses resulting from the action of drugs like ibogaine and scopolamine.

It is clear that the pharmacologically active constituents of ololiuqui are the isomeric lysergic acid amides. Intramuscular doses of 0.5 mg., or larger oral doses, of *d*-lysergic acid amide produce apathy, decreased motor activity, and tiredness, culminating in a clouding of consciousness (Solms, 1956; Hofmann, 1963b). Oral doses of 2 mg. of isolysergic acid amide are reported to produce a feeling of mental emptiness and total detachment from the outside world. Heim and his colleagues suggest that the overall effects of ololiuqui are due to these two compounds, the *d*-lysergic acid amide giving intoxication with strong autonomic side-effects and the *d*-isolysergic acid amide producing some euphoria, synaesthesia, and altered time experience. Certainly elymoclavine, lysergol, chanoclavine, and ergometrine produce no psychic changes in man (Isbell and Gorodetzky, 1966; Hofmann, 1968), though the first two do produce central excitation in animals (Yui and Takeo, 1958). Moreover, the time-course of absorption and distribution of *d*-isolysergic acid amide in rat brain exactly paralleled the course of behavioural aberrations produced by intraperitoneal doses of 5 mg./kg. (Vogel, Carapellotti, Evans, and Der Marderosian, 1972).

It is possible that other constituents of ololiuqui may possess central actions. Thus, glucosides have been isolated which are five times as potent as central stimulants as the crude alkaloid extracts of *Rivea corymbosa* (Cook and Kieland, 1962; Perezamador, Jiminez, Herren, and Flores, 1964). However, Hoffer and Osmond (1967) report that they produced only sedative and narcotic effects upon self-administration at doses of 5 mg. (p.o.).

The derivatives of lysergic acid present in ololiuqui are widely distributed throughout the *Ipomoea* and other convolvulaceous species (Der Marderosian, 1967). Their presence in the seeds of ornamental Morning Glories has led to considerable self-experimentation with these potential hallucinogens which bear no legal restriction on their use. Though there has been no systematic psychopharmacological investigation of these plants, several cases of morning glory seed intoxication have been reported in the United States (Cohen, 1964; Ingram, 1964; Fink, Goldman, and Lyons, 1966; Whelan, Bennett, and Moeller, 1968). One was serious enough to provoke suicide and several required hospitalization; the danger has been underlined that latent psychoses can be activated by excessive ingestion of the seeds. The subjects reported autonomic effects such as nausea, flushed skin, extremely dilated pupils, low

blood-pressure, and increased pulse-rate, following ingestion of 150–300 seeds. Hallucinations and visions were occasionally present, but the chief psychic changes were apathy and concern with the reality of people and objects. The unpleasant nature of the psychic changes produced by Morning Glory seeds makes it unlikely that they will be used widely as intoxicants, particularly since Der

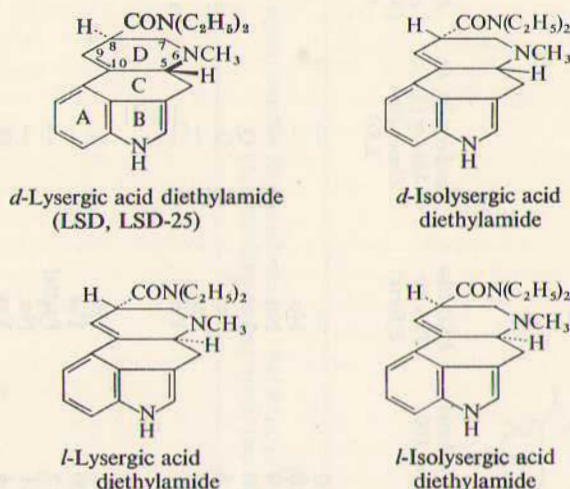


Fig. 4.4.—The four stereoisomers of lysergic acid diethylamide. Only LSD produces psychic effects in man.

Marderosian has pointed out the possibility of ergot poisoning if large doses are taken. Five-hundred seeds of certain ornamental *Ipomoea* varieties contain as much as 1 mg. of ergometrine, which is usually considered to be an effective oxytocic in doses as low as 0.2–0.5 mg.

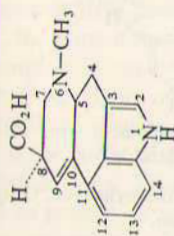
2. LYSERGIC ACID DIETHYLAMIDE

Structure–Activity Relationships

d-Lysergic acid diethylamide (LSD, LSD-25) does not occur in nature. It was produced synthetically by a process analogous to that used to prepare ergometrine and other amide derivatives of lysergic acid (Stoll and Hofmann, 1943). The original synthesis used hydrazine to cleave ergot alkaloids to lysergic acid hydrazide, which was treated with nitrous acid to give an azide followed by acylation of

Table 4.3.—COMPARATIVE HALLUCINOGENIC POTENCIES IN MAN OF DERIVATIVES OF D-LYSERGIC ACID*

Compound	Dose equivalent to 1 µg/kg. (p.o.) of LSD	Potency relative to LSD = 100	LSD-like Psychic Effects	Quicker (Q), or Slower (S) Onset than LSD	Longer (L) or Shorter (S) Duration than LSD
AMIDES					
Diethylamide (LSD)	1.0	100	—	—	—
<i>l</i> -lysergic acid diethylamide	>70	0	No	—	—
<i>d</i> -isolysergic acid diethylamide	>50	0	No	—	—
Dimethylamidet	10	10	Yes	Q	S
Monoethylamide	20	5	Yes	Q	S
Pyrrolidide	10	10	Yes	—	S
Morpholide	9	11	Yes	—	S
1- <i>and</i> -2-SUBSTITUTED COMPOUNDS					
1-methyl, diethylamide	3	33	Yes	S	S
1-acetyl, diethylamide	1	100	Yes	—	—
2-bromo, diethylamide	>86	<2	Partial	—	S
1-methyl-2-bromo, diethylamide	>175	<1	No	—	—
1-methyl, monoethylamide	25	4	Yes	Q	S
1-acetyl, monoethylamide	15	7	Yes	Q	S
1-methyl, pyrrolidide	>20	<5	Partial	Q	S



MISCELLANEOUS	8	12·5	Yes	S	L
<i>d</i> -2,3-dihydrolysergic acid diethylamide					
<i>d</i> -9,10-dihydrolysergic acid diethylamide	> 50	0	No	—	—
<i>d</i> -9,10-dihydro-10-hydroxy-lysergic acid diethylamide (Lumilysergic acid diethylamide)	> 50	0	No	—	—
<i>bis</i> -2,2'-(<i>d</i> -lysergic acid diethylamide) disulphide	> 50	0	No	—	—

*Compiled from Isbell, Miner, and Logan, 1959; Gorodetzky and Isbell, 1964; Hofmann, 1968.

†Rothlin (1957b) states that this compound is inactive at doses of 50 µg./kg., and reports similar negative results for the monomethyl, and the mono- and di-propyl and butyl amides of *d*-lysergic acid.



dimethylamine. The method is not stereospecific and requires chromatographic separation of isomeric compounds, but it was used to prepare most of the amides of lysergic acid discussed in this section. The most advantageous procedure for the preparation of LSD is to treat *d*-lysergic acid with sulphur trioxide in dimethylformamide at low temperature followed by reaction with dimethylamine and hydrolysis; the yield is virtually quantitative, the entire reaction takes less than an hour, and the product is a single isomer (Garbrecht, 1959).

Studies of structure-activity relationships have tended to concentrate on the *d*-lysergic acid series, because its diethylamide is the only one of the four possible stereoisomers (Fig. 4.4) which produces profound psychic changes in man (Rothlin, 1957a, b; Isbell, Miner, and Logan, 1959; Hofmann, 1968). However, synthetic difficulties have precluded any route which does not involve the preformed lysergic acid skeleton, and molecular modifications of LSD are limited to manipulation of this skeleton. They include, in addition to variations in the spatial arrangements at C-5 and C-8, variations in the acid amide residue, saturation of the double bonds at C-9/C-10 or C-2/C-3, and substitution of the indole ring system at C-1 and C-2 (Table 4.3).

Of all the possible changes that have been made in the LSD molecule, only two, acetylation or methylation of the indolic imino group, have yielded compounds of comparable potency to the parent hallucinogen (Table 4.3). Their high activity may well be due to the ease with which they are converted to LSD, particularly hydrolysis of the *l*-acetyl derivative. Various attempts to simplify the LSD structure by breaking it down into molecular fragments have, with the exception of the tryptamines, generally led to profoundly deleterious effects on the hallucinogenic activity (Campaigne and Knapp, 1971). One other compound of interest is *d*-2,3-dihydrolysergic acid diethylamide, which is from one-sixth to one-eighth as potent as LSD but with a slower onset and a longer duration of action; it is not known whether this reflects *in vivo* dehydrogenation to LSD (Gorodetzky and Isbell, 1964). The general trend of hallucinogenic activity in man parallels that of sympathetic stimulation in animals (Hofmann, 1968). Those compounds which are most effective in man are also effective in producing mydriasis, piloerection, salivation, hyperthermia, and other signs of excitation in animals. There is little correlation between hallucinogenic potency in man and antagonism to 5-hydroxytryptamine in animals or *in vitro*, where compounds with high anti-5HT activities can be either poor (for example, 2-bromolysergic acid diethylamide) or potent (1-methyllysergic acid diethylamide) hallucinogens.

Table 4.4.—ACTIVITY OF LSD COMPARED TO OTHER HALLUCINOGENS*

Compound	Approx. Effective Dose (p.o.) (Man)†	ED ₅₀ (i.p.) Size Discrimination (Squirrel monkey)‡	ED ₅₀ (i.p.) Production of Swimming Latency (Rats)§	ED ₅₀ (s.c.) Production of Head Twitches (Mice)	Approx. Dose (i.v.) for 1° rise in Rectal Temperature (Rabbits)
LSD	0.0004 (0.1)	0.15	1.9	0.14	0.006
Psilocybin	0.6 (12)	2.9	8.7	4	0.12
DOM**	0.34 (5)	2.9	9.5	—	0.2
Mescaline	27 (400)	82.2	>31	45	344

* All doses are in μ moles/kg.

† Figures in parentheses are total oral doses (mg.) in man.

‡ From Uyeno, 1969.

§ From Uyeno, 1968, 1971.

|| From Corne and Pickering, 1967.

¶ From Horita and Hill, 1973; Aldous and others, 1974.

** DOM is 2,5-dimethoxy-4-methylamphetamine.

Pharmacology

Since the accidental discovery by Hofmann in 1943 of the extraordinary psychic changes produced by LSD, an extensive literature has built up dealing with its effects in animals and in both normal and mentally ill human subjects. It is beyond the scope of this section to list them all, and readers are directed for comprehensive coverage to the relatively modern books of Hoffer and Osmond (1967) and Efron (1968), and the review of Cohen (1971). The sheer breadth of investigations with LSD is indicated by its binding to DNA (Yielding and Sternglantz, 1968), its lethal effect at 297 mg. (i.m.) in the elephant (West, Pierce, and Thomas, 1962), its production of a nose-up tail-down position in the Siamese fighting fish (Gettner, Rolo, and Abramson, 1964), and the correlation of hallucinogenic potency in lysergic acid derivatives with motility in liver flukes (Beernink, Nelson, and Mansour, 1963). It seems that no stone has been left unturned.

The original dose of LSD taken by Hofmann in 1943 was 250 µg. (Hofmann, 1961a), although the effective oral dose for the production of psychic phenomena in normal subjects is 0.5–1.0 µg./kg. Amounts as low as 0.02 µg./kg. can induce discernible effects in most individuals, and as much as 10 mg. has been ingested without fatal outcome (Cohen, 1971); recent reports (Tijo, Pahnke, and Kurland, 1969) give 50 µg. as a low dose and 450 µg. as a high dose. These doses produce, in varying degrees, the classical changes in mood, thought, and perception described in Chapter 1. LSD is therefore the most potent hallucinogen, and indeed one of the most potent drugs of any type, known to man; the general trend of potency between LSD, psilocybin, DOM, and mescaline is reproduced in a variety of animal behavioural tests (*Table 4.4*).

In addition to the psychic phenomena, LSD produces hyperflexia, nausea, tremor, muscular weakness, hyperthermia, and, most commonly, mydriasis. Peripheral and autonomic effects are normally insignificant in man at the hallucinogenic dose levels, but animals

Table 4.5.—TOXICITY OF LSD IN VARIOUS SPECIES (after Cohen, 1971)

<i>Animal</i>	<i>Body-weight (kg.)</i>	<i>LD₅₀ (mg./kg.)</i>	<i>Brain Weight (g.)</i>
Mouse	0.035	46 (i.v.)	0.5
Rat	0.5	16.5 (i.v.)	1.7
Rabbit	3.5	0.3 (i.v.)	85
Man	70	0.2 (p.o.)*	1400
Elephant	4500	0.15 (i.m.)*	3600

*Estimated values.

usually respond with a syndrome of general excitation including prominent hyperthermia, piloerection, mydriasis, and salivation. Death can result from respiratory failure if high doses of LSD are given to animals but the therapeutic ratio is high, with the LD_{50} for man being estimated to be about 14 mg. (Hoffer and Osmond, 1967). The degree of toxicity varies widely with the species, the rabbit being particularly sensitive, and seems to correlate rather better with brain than with body weight (Table 4.5).

In chronic experiments, rats tolerated 2.5 mg./kg. (i.v.) daily for 30 days with no development of cumulative effects or of tolerance (Hofmann, 1968). Nevertheless, tachyphylaxis develops rapidly to the psychic effects of LSD in man, with complete tolerance within a few days. Cross-tolerance occurs between all members of the lysergic acid series, and between LSD, mescaline, and psilocybin; both tolerance and cross-tolerance are lost within a few days of discontinuance of the hallucinogenic drug (Brawley and Duffield, 1972). It is interesting to note that mice can be immunized against the effects of intravenous LSD by treatment with a protein derivatized with lysergic acid, suggesting the possible involvement of antibody production in the mechanism of tolerance (Voss and Berger, 1972).

Absorption and Metabolism

LSD is equally effective whatever the route of administration, although it is normally taken by mouth in the form of tablets or aqueous solutions of its tartrate salt. The onset of symptoms varies with the route, oral administration producing effects within 30–90 minutes, intramuscular injection within 10 minutes, and intravenous injection within a few minutes. Three methods have been used to study the distribution of LSD, based respectively on bioassay of its antagonism to the action of serotonin (Lanz, Cerletti, and Rothlin, 1955), radioactive assay of ^{14}C -labelled LSD (Stoll, Rothlin, Rutschmann, and Schalch, 1955), and spectrofluorometric estimation of its concentration in tissue extracts (Axelrod, Brady, Witkop, and Evarts, 1957). The accuracy of the last can be improved to detect LSD levels in man as low as 1–2 ng./ml. by irradiating half of the extracts with ultraviolet light prior to fluorometric estimation; this treatment catalyzes the hydration of LSD to the non-fluorescent lumi-LSD giving an effective blank (Upshall and Wailling, 1972). The same results are obtained by all three methods of estimation.

LSD is rapidly absorbed from the gastrointestinal tract and disappears quickly from the blood to be assimilated into most of the tissues. It is almost completely metabolized in the body, chiefly in the liver, from whence it is secreted in the bile and excreted via the gut, with negligible amounts of unchanged drug being found in the urine

or faeces. The half-life in rodents is less than 10 minutes, but rats and mice show an enormous capacity to deal with LSD and may be considered to be in a state of almost permanent tolerance; in the cat and monkey the half-life is 130 minutes and 100 minutes respectively. In man the rate of disappearance of LSD from plasma as measured by spectrofluorometry gives a half-life of 175 minutes (Aghajanian and Bing, 1964), a value which was later corrected to 109 minutes based upon a more detailed analysis of the pharmacokinetics (Wagner, Aghajanian, and Bing, 1968). Following intravenous injection of 2 $\mu\text{g.}/\text{kg.}$, plasma levels reached 7 ng./ml. within 30 minutes and gradually declined over 8 hours to 2 ng./ml., paralleling the general pattern of psychic effects. It is therefore likely that LSD is centrally active *per se* and not as an initiator of a sequence of aberrant neurochemical reactions, a possibility that has been suggested on the basis of extrapolation of rodent metabolic data to man.

There is no specific concentration of LSD into the brain, whatever the route of administration. In most species, including man, only 1–1.5 per cent of absorbed drug reaches the brain and is soon detectable in the cerebrospinal fluid; following a typical human dose of 100 $\mu\text{g.}$, only 1 $\mu\text{g.}$ is distributed to the brain. Nevertheless, this is probably sufficient since qualitatively and quantitatively similar behavioural changes are obtained in rats when LSD is given either intravenously or intracerebrally, the effects of the latter route merely appearing earlier (Haley and Rutschmann, 1957). In the rat (Diab, Freedman, and Roth, 1971), LSD, 1.7 $\mu\text{g.}/\text{kg.}$ intravenously, penetrates the brain within 5 minutes and reaches maximum concentration in 15 minutes, disappearing after approximately 1 hour. Free drug was distributed generally throughout the brain, but LSD was bound specifically to neurons in the cortex, caudate nucleus, mid-brain, and medulla. This specific localization is confirmed by *in vitro* studies of the binding of LSD to subcellular fractions of rat brain (Farrow and Van Vunakis, 1972), and provides evidence for the association of serotonergic neurons and post-synaptic localization of LSD in serotonin granules in the mechanism of action of the hallucinogen (*see* Chapter 8). However, there was little evidence of bound LSD in studies of its distribution in the brain of squirrel monkeys receiving 2 mg./kg. (*i.v.*) (Snyder and Revich, 1966), most of the drug being in the supernatant fractions. Thus, 20 minutes after injection, the blood, cerebral cortex, cerebellum, and brain-stem all had approximately equal concentrations, with 1.5 times as much in the thalamus and extrapyramidal system, 2–3 times as much in the hypothalamus and limbic systems, 2–5 times as much in the auditory and visual cortex, 5–7 times as much in the posterior pituitary and pineal, and 10 times as much in the anterior pituitary. These variable

concentrations within the brain may explain the psychic phenomena produced by LSD. Thus, the limbic system is involved in emotionality, the hypothalamus with the overall elaboration of emotion, and the anterior pituitary with the stress response. In human subjects with subcortically implanted electrodes, LSD induces paroxysmal E.E.G. activation of the limbic system and, particularly, the posterior hypothalamus. Finally, inhibition of synaptic transmission in visual reflex areas such as the lateral geniculate body could impair perception (Cohen, 1971; Brawley and Duffield, 1972) (see Chapter 8).

The lysergic acid nucleus of LSD is not cleaved or degraded *in vivo*, and little oxidation of the substituted amide side-chain occurs. Boyd (1959) found that only 4 per cent of the drug was degraded to carbon dioxide over the course of 12 hours in the rat, while over 80 per cent of the dose appeared in the bile within 3 hours, principally as the glucuronides of 12- (or possibly 13-)hydroxylysergic acid diethylamide and 12-(13?) hydroxyisolysergic acid diethylamide (Slaytor and Wright, 1962; Szára, 1963). Though LSD is metabolized *in vitro* by guinea-pig liver microsomes to its 2-oxo derivative, this metabolite has not been found in other species (Axelrod and others, 1957). The high potency and great rapidity of action of LSD makes it unlikely that its action is due to an active metabolite, and these products undoubtedly represent detoxification routes.

Biochemical Effects

The symptoms produced by LSD are very dependent on the type of person involved, and certain people seem much more resistant to its effects than do others. Schizophrenics have a markedly high threshold of responsiveness to the drug, chronic alcoholics may often require more than ordinary doses, while those individuals who wish to resist its effects consciously or unconsciously may be able to prevent average doses from having the usual impact (Hoffer and Osmond, 1967). These factors, coupled with investigations of the mode of action of LSD, have led to extensive study of its biochemical effects in man and in animals. Unfortunately, many of the results are contradictory and often not self-consistent; for example, LSD is reported to inhibit, to increase, and to have no effect upon the activity of human brain pseudocholinesterase (Giarman and Freedman, 1965; Hofmann, 1968).

Only two biochemical systems are reported to be affected by LSD in man. The drug diminishes excretion of inorganic phosphate and increases the free fatty acid content of the plasma, possibly as a result of non-specific stress (Hollister and Moore, 1965). Injection of adrenocorticoids during the period of action of LSD further

enhances the excretion of phosphate, a pattern also seen in schizophrenics who have received no LSD. The hallucinogen has no significant effect in man on the following parameters: cerebral blood-flow, cerebral vascular resistance, oxygen or glucose utilization, or respiratory quotient; levels of serum or plasma creatinine, urea, sodium chloride, cholesterol, and total lipid; and activities of serum caeruloplasmin or pseudocholinesterase. LSD produces mild hyperglycaemia, possibly as a consequence of an increased metabolic rate resulting from its inhibition of oxidative phosphorylation in the brain coupled with increased oxygen consumption in the whole organism.

Perhaps the most important biochemical findings are those which relate LSD to serotonin-containing systems (Ahlborg, Holmstedt, and Lindgren, 1968; Cohen, 1971; Brawley and Duffield, 1972). These are discussed fully in Chapter 8, and it is sufficient here to indicate that LSD decreases the turnover of serotonin in the brain and thus increases brain levels of the neurotransmitter. The coincidence of peak rise in brain serotonin, plasma half-life of LSD, and termination of psychic or behavioural effects in man and animals, suggests an involvement of this biochemical effect in the mode of action of the drug. LSD thus decreases the availability of serotonin at the points where it acts in the brain, since the increased levels of the neurotransmitter are intracellular and therefore ineffective at the synapses.

Therapeutic Uses of LSD and Adverse Reactions

When the psychic effects of LSD became widely known in the 1950s, the interest of physicians was such that within a decade the drug had an established place in psychotherapy (Hoffer and Osmond, 1967; Freedman, 1968). It was used both as an adjunct to conventional psychotherapy, to induce loosening of unconscious defence mechanisms, and as a highly specialized form of brief intensive psychotherapy, to make the subject aware of new and different avenues for personality change and development. By 1960, LSD had been used in the treatment of every type of mental affliction and character disorder, ranging from acute schizophrenia and drug addiction to alcoholism and homosexuality. Most of these studies have reported promising results, but it is clear that where carefully controlled studies have been performed, be they for mental illness (Hollister, Degan, and Schultz, 1962; Robinson, Davis, Sack, and Morrissey, 1963) or for alcoholism (Hollister, Shelton, and Krieger, 1969; Ludwig, Levine, Stark and Lazar, 1969), there is little difference in the improvement of patients receiving LSD, placebo, or no drug at all. In recent years LSD has fallen from favour and is

no longer regarded as the panacea for all mental ills; this rejection seems to be based more on a general reaction to the public image of the drug than to scientific evaluation of the available results. Controlled clinical studies of the drug are still required before its place, if any, in psychotherapy can be properly assessed.

LSD is a dangerous drug and should be given to humans only under carefully controlled conditions and with experienced medical supervision. Nevertheless, its use spread during the 1950s from the research laboratory to practising physicians, who dispensed it to themselves, their patients, and their friends and relatives with a casualness that belied its toxic potential. A general attitude arose that LSD was a reasonably safe drug and its use spread further to the general public, when reports of adverse reactions started to appear with regularity. It is difficult to decide whether many of these are due to LSD or to other constituents of the often impure illicit drug samples, but the general consensus of opinion is now that LSD does produce three overlapping categories of adverse reactions—acute reactions, recurrent reactions in which there is a recurrence of symptoms without reingestion of the drug, and prolonged reactions (Meyer, 1969). The incidence of such reactions is unknown, but they account for about 1 per cent of the total psychiatric admissions to U.S. city hospitals.

Acute reactions arise concomitantly with the ingestion of LSD and are short-lived. They include a psychotoxic reaction resembling acute paranoia, in which the subject has grandiose or persecutory illusions, and a panic reaction, which is a response of the subject to the drug-induced symptoms. These effects can appear in both naive and experienced drug users, and can recur several weeks or months later without further ingestion of the drug. The recurrent reactions may last for only a few seconds or for an extended period of time, and occur most frequently in subjects who are particularly susceptible to suggestion. Chlorpromazine is the recommended treatment for those 'bad trips' (Consroe, 1973), although it is not a complete antagonist and can exacerbate the symptoms of other drugs which may be present in illicit samples of LSD or be mistaken for LSD. Usually, the dose is 25–50 mg. intramuscularly, repeated every 30 minutes until the situation is under control. Nicotinic acid is recommended by Hoffer and Osmond (1967), who consider that thrice-daily doses of 1–2 g. of the vitamin are particularly useful for preventing recurrent reactions in potentially susceptible subjects as well as for treating prolonged reactions to LSD. Habitual use of LSD has been reported to produce chronic anxiety or psychotic states, and may arise in persons who were not psychotic prior to the taking of the drug.

LSD and Genetic Damage

The toxicity of LSD may also manifest itself in mutagenic and teratogenic effects, and particularly in the production of chromosomal abnormalities (Dishotsky, Loughman, Mogar, and Lipscomb, 1971; Long, 1972). Suspicions were originally aroused by the report of Cohen and his colleagues (Cohen, Marinello, and Back, 1967) describing a marked increase in chromosomal abnormalities in human leucocytes which had been incubated with LSD in tissue cultures, and they were apparently confirmed in humans who had been regular users of the drug (Cohen, Hirshkorn, and Frosch, 1967). Accusations of teratogenicity in rats (Alexander, Miles, and Gold, 1967), mice (Auerbach and Rudowski, 1967), hamsters (Geber, 1967), and man (Zellweger, McDonald, and Abbo, 1967; Hecht, Beals, Lees, Jolly, and Roberts, 1968; Carakushansky, Neu, and Gardner, 1969) rapidly followed. The frequent lack of scientific objectivity in many of these reports is incredible, particularly where human toxicity has been based upon one or two cases who have ingested not only LSD but also every other psychotropic agent. There have been a tremendous number of conflicting reports during the last five years and it is more instructive to summarize the results than to refer to every individual paper; the reviews by Dishotsky and others (1971) and by Long (1972) should be consulted for over 100 references to the original literature.

Chromosomal breakage after exposure to LSD has been observed in 6 of 9 *in vitro* studies, the damage arising during or after DNA synthesis. With one exception it was the result of concentrations of drug and durations of exposure which cannot be achieved in man with non-lethal doses. The absence of a dose-response relationship, the lack of *in vitro* detoxification mechanisms for LSD, and the similar aberrations produced by such innocuous events as changes in temperature or oxygen pressure or by common substances like aspirin, caffeine, and even water, cast serious doubt upon the relevance of the positive results. A total of 310 human subjects have been examined for chromosomal damage, with the frequency being triple among illicit drug users (184 subjects) compared with those who received chemically pure LSD (126 subjects). Of all the subjects reported to have chromosome damage, only 18 of the 108 were exposed only to pure LSD, and it can be concluded that such damage, when found, is more related to the effects of drug abuse in general than to LSD in particular. Pure LSD ingested in the normal doses does not produce chromosomal aberrations that can be detected by available methods.

There appears to be no causal relationship between LSD use and cancer, and there is no increase in the incidence of neoplasms among

regular LSD users over that in the general population. LSD may, however, be a weak mutagen, effective only in extremely high doses which are unlikely to be achieved in human subjects. Thus, threshold mutagenic responses in *Drosophila* were manifest only at levels of 2000–10000 $\mu\text{g./ml.}$ with no effects at low doses up to 500 $\mu\text{g.}$ Circular dichroism experiments suggest that LSD may directly interact with DNA to produce conformational changes in the DNA helix; such changes are unlikely to provide a sufficient decrease in internal stability to cause breakage of chromosomes but they may be the physical basis of the weak mutagenicity.

Studies of the teratogenic hazards of LSD in animals indicate a wide variation of individual, strain, and species susceptibility to its effects. The most comprehensive report (Roux, Dupuis, and Aubry, 1970) using rats, hamsters, and mice, indicates that there is no significant increase in abortifacient, teratogenic, or growth-depressing effects. Nevertheless, the overall view seems to be that a slightly higher incidence of such effects can arise if LSD is given at a highly specific time early in gestation, and it is significant that the drug is almost five times as effective at crossing the placental barrier in mice during early than it is during late pregnancy (Idänpään-Heikkilä and Schoolar, 1969). The incidence of early spontaneous abortion also seems to be slightly elevated in human pregnancies, although the incidence appears to be somewhat lower among those exposed to pure LSD (15 per cent) than it is among either the general population (20 per cent) or those exposed to illicit LSD (37 per cent) (McGlothlin, Sparkes, and Arnold, 1970). There are no reports of malformed children born to women who ingested pure LSD either before or during pregnancy, but 6 cases are recorded of malformations associated with exposure to illicit LSD. There is little evidence, therefore, that LSD is teratogenic in man, notwithstanding that the use of any drug during pregnancy requires that its potential benefits significantly outweigh its potential hazards (Dishotsky and others, 1971; Long, 1972).

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Chapter 5

Cannabis

I. INTRODUCTION

Cannabis sativa L., the Indian hemp plant, was one of the earliest plants used by man for purposes other than food. The fibre in its stem (hemp) and the oil in its seeds have economic value, but it is with the hallucinogenic drug extracted from various parts of the plant that this chapter is concerned. Selection of the plants for stronger fibre or higher oil content or increased drug production have been carried out in many parts of the world; these aspects are discussed by Boyce (1900), Bouquet (1950), and Schultes (1970). The plant appears to be indigenous to the plains of Central Asia north of the Himalayas (Vavilov, 1926) but it has spread to many other regions including India, South-East Asia, Europe, and the Americas. It grows best on alluvial soils and on others with a low clay content (Haney and Bazzaz, 1970).

Preparations of *Cannabis sativa* have been used medicinally by man for at least 5000 years (Way, 1971), although it was not introduced into Europe until 1500 B.C. and reached the Americas only with Spanish explorers and English colonists (Schultes, 1970). The earliest recorded use of cannabis extracts is in Chinese medicine to produce surgical analgesia, but there are no reports in these early writings of the psychotropic properties. Interestingly, Rabelais also did not mention them in his account in 1546 of the 'pantegruelion herb' (*Cannabis sativa*), but he recorded that the seeds were beloved by birds and eaten by the Greeks (Schultes, 1970). It is perhaps of significance that only trace amounts of the active principles of cannabis are present in the seeds (Krejci, 1970; Waller and Scigliano, 1970). There has been considerable controversy as to the analgesic properties of cannabis extracts (Garattini, 1965), but, nevertheless, they enjoyed in the form of hashish a wide popularity in the nineteenth century. Largely as a result of the writings of Aubert-Roche (1843) and Moreau (1845), hashish was used to treat a variety

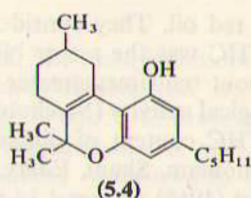
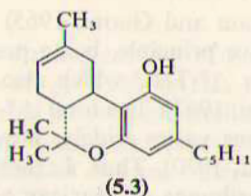
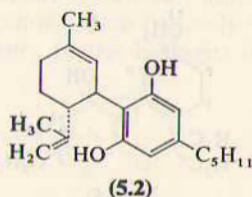
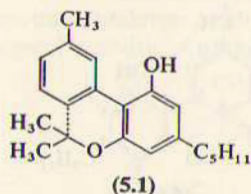
of conditions including coughs, rheumatism, asthma, tetanus, and mental depression. With the advent of more useful and specific drugs for these purposes, and the realization that hashish produced undesirable side-effects, its use declined and today it has no place in medicine.

Various products of cannabis plants have been used for many centuries for their euphoriant properties, particularly in the Middle and Far East. The number of users of the drugs in 1957 was estimated to be 200 million; presumably it is much higher today (Gershon, 1970). The products have innumerable names depending not only on the region of the world in which they are prepared but also on the part of the plant used and on the method of preparation. Basically there are two types of material, the exudate or resin from the flowering tops or leaves, known in the Middle East and North Africa as hashish and in the Far East as charas, and the chopped leaves and stalks, best known as marihuana. A form of hashish manufactured from the entire flowering top is known as *ganga* in India, *kif* in North Africa, *dagga* in South America, and *macunha* in Brazil (Brown, 1972). Even these terms are not used consistently, however, the word marihuana often being applied indiscriminately to any cannabis product as are the popular colloquial words like *pot*, *weed*, and *grass*.

Cannabis is most commonly smoked, by which route it produces the most intense intoxication (Watt, 1965), although it is also effective by mouth. There have been reports of its use as a snuff but its effectiveness by the nasal route has not been confirmed. In the Far East marihuana is brewed as a tea, while in Jamaica it is cooked with or embedded in food. In North Africa and the Middle East it is often made into a sweetmeat known as *majoon* (Goode, 1969).

The active principles of cannabis were shown by Smith and Smith (1847) to be contained in a non-alkaloidal, alkali-insoluble, high-boiling fraction. Wood, Spivey, and Easterfield (1899) identified from this impure fraction, known as 'red oil', a single substance which they named *cannabinol*, the structure of which (5.1) was elucidated some 30 years later (Cahn, 1930, 1931, 1932, 1933). A new substance, *cannabidiol* (5.2), was isolated by Adams, Hunt, and Clark (1940) in an attempt to repeat Cahn's work, and in the same year Adams, Pease, and Clark isolated and crystallized *cannabinol* from its natural source. It soon became apparent that neither *cannabinol* nor *cannabidiol* was responsible for the biological activity of red oil, and attention was focused on the tetrahydrocannabinols (THCs) which had been prepared as intermediates in syntheses designed to establish the structure of *cannabinol* (Adams, 1941; Todd, 1946). Adams's group (Adams, Pease, Caim, and Clark, 1940)

showed that under acid conditions cannabidiol cyclizes to form mixtures of optically active tetrahydrocannabinols, which were called low and high rotating compounds. The high rotating compound, which possessed biological activity, was shown to be Δ^8 -THC (5.3) (Adams and Baker, 1940), a dibenzopyran derivative existing in the *trans*-conformation as do all the naturally occurring cannabinoids. Adams and Baker (1940) also synthesized $\Delta^{6a,10a}$ -THC (5.4), as did Ghosh, Todd, and Wilkinson, in the same year. This was claimed to have about one-eighth the activity of Δ^8 -THC



in man and was used widely as the standard substance in animal tests on cannabinol derivatives. Other workers, notably Isbell and his colleagues, cast some doubt on the activity of the compound, especially when administered to man by smoking (Isbell, Gorodetsky, Jasinski, Claussen, von Spulack, and Korte, 1967).

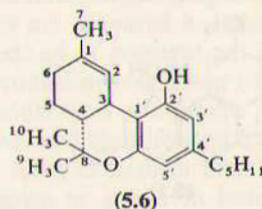
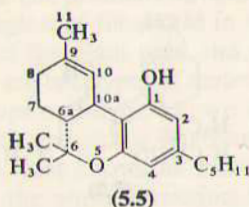
The fact that the possibly inactive $\Delta^{6a,10a}$ -THC was used as a standard and that mixtures of isomeric compounds as well as plant extracts and synthetic compounds (often all designated as tetrahydrocannabinols) were used in most of the early studies renders a good deal of the biological work prior to 1965 open to serious doubt. Moreover, the biological testing methods were of dubious value. Most commonly used were the dog ataxia test (Walton, 1938) and the so-called Gayer test (Gayer, 1928) which depends upon the development of corneal anaesthesia in mice, rats, and rabbits.

More confusion has arisen from the use of different numbering systems for the structurally complex tetrahydrocannabinols. The two main systems, both in current use, are based on formal pyran-type numbering or on monoterpenoid numbering. Thus, the same

compound may be designated, for example, as Δ^9 -THC (5.5, pyran-type numbering) or as Δ^1 -THC (5.6, monoterpenoid numbering). The formal pyran-type numbering will be used throughout this book.

CONSTITUENTS OF CANNABIS

In the early 1960s, Mechoulam and his co-workers, using modern chromatographic techniques, were able to isolate nine compounds

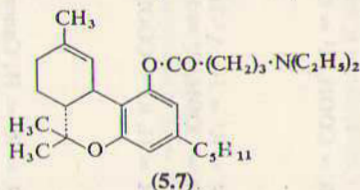


from red oil. They considered (Mechoulam and Gaoni, 1965) that Δ^9 -THC was the major biologically active principle, being present in about ten times greater amounts than Δ^8 -THC which also had biological activity (Mechoulam and Gaoni, 1967). The total Δ^9 - and Δ^8 -THC content of different preparations varies widely, however (Mechoulam, Shani, Edery, and Grunfeld, 1970). Thus, Lerner and Zeffert (1968) analysed 14 samples of marihuana of Mexican origin by gas chromatography. These samples, comprising a mixture of leaves, stems, and seeds, contained an average of 1.2 per cent of THC by weight; of this 0.4 per cent was the Δ^8 -isomer. Freshly prepared red oil from hashish had 31 per cent of THC content, of which 3 per cent was the Δ^8 -isomer; by comparison a 4-year old sample of red oil had only 0.8 per cent THC, of which 60 per cent was the Δ^8 -isomer. This may seem to confirm the view expressed by Hively, Mosher, and Hoffman (1966) that isomerization of Δ^9 -THC to Δ^8 -THC occurs at room temperature under normal conditions. Another possibility is that preferential oxidation of the Δ^9 -isomer occurs since it is not certain that the absolute amount of the Δ^8 -isomer increases with time (Taylor, Lenard, and Shvo, 1966).

More recently, many more compounds have been identified in various cannabis extracts. In a recent publication, Waller (1971) lists 16 such compounds, which are shown in Table 5.1; they are known collectively as cannabinoids.

Synthetic methods are now available for most of the naturally occurring cannabinoids. Petrzilka and Sikemeir (1967a, b)

and Petržilka, Haefliger, and Sikemeir (1969) described a stepwise synthesis of the THC_s, which Razdan and his colleagues (1970) modified into a single-stage synthesis of Δ^8 -THC. The latter could then be converted after purification to Δ^9 -THC, via a process of hydrochlorination and dehydrochlorination. These pure synthetic compounds are identical with naturally occurring THC_s and are now available for biological studies. The result has been a tremendous proliferation of work in the cannabis field in the past few years, though some practical problems still exist. For example, Δ^9 -THC is readily isomerized to Δ^8 -THC under acidic conditions, and both compounds undergo oxidation to cannabinol, which has only weak biological activity. Another major difficulty to the biologist is the



poor water-solubility of the cannabinoids. The diethylaminobutyric ester of Δ^9 -THC (ADL 1137, 5.7) is water-soluble and has been reported to produce similar pharmacological effects to those of the parent compound (Howes, 1970). The preparation has also been reported of several other nitrogen-containing water-soluble esters of Δ^9 -THC (Zitko, Howes, Razdan, Dalzell, Sheehan, and Pars, 1972). Compounds such as these may assist in future investigations, though it should always be borne in mind that the effects of pure synthetic compounds may not be identical with those of natural extracts of various compositions.

The evidence currently available suggests that Δ^8 - and Δ^9 -THC are the only constituents of cannabis that are active as hallucinogens in man, although some workers dispute this view. For example, Karniol and Carlini (1972) claimed that the content of Δ^9 -THC did not account for all the biological activity of some Brazilian marihuana samples. This opinion was based on a number of animal studies as well as a human experiments. Nevertheless, the weight of evidence suggests that it is unlikely that any other as yet unidentified cannabis constituents are responsible for the overall effects. Moreover, neither cannabinol nor cannabidiol produce any psychic effects in man, even when given intravenously in doses of 30 mg. or orally in doses of 400 mg. (Hollister, 1973). However, cannabidiol can interact with Δ^9 -THC; in rabbits, mice, and rats it is claimed to potentiate the depressant effects but antagonize the excitatory effects of Δ^9 -THC (Karniol and Carlini, 1973).

Table 5.1.—CANNABINOIDS OCCURRING IN MARIJUANA (from Waller, 1971)

General Names	General Formula	Individual Compounds
Cannabidiol and derivatives		$R = R^1 = H$; Cannabidiol $R = COOH, R^1 = H$; Cannabidiolic acid $R = H, R^1 = CH_3$; Cannabidiol monomethyl ether $R = COOH, R^1 = CH_3$; Cannabidiolic acid monomethyl ether
Δ^9 -Tetrahydrocannabinol and derivatives		$R = R^1 = H$; Δ^9-Tetrahydrocannabinol $R = COOH, R^1 = H$; Δ^9-Tetrahydrocannabinolic acid (A) $R = H, R^1 = COOH$; Δ^9-Tetrahydrocannabinolic acid (B)
Cannabigerol and derivatives		$R = R^1 = H$; Cannabigerol $R = COOH, R^1 = H$; Cannabigerolic acid $R = H, R^1 = CH_3$; Cannabigerol monomethyl ether $R = COOH, R^1 = CH_3$; Cannabigerolic acid monomethyl ether

Table 5.1.—CANNABINOIDS OCCURRING IN MARIHUANA (from Waller, 1971)—*cont.*

General names	General Formula	Individual Compounds
Cannabinol and derivatives		R = H; Cannabinol R = COOH; Cannabinolic acid
Cannabichromene and derivatives		R = H; Cannabichromene R = COOH; Cannabichromenic acid
Cannabicyclol		Cannabicyclol (Cannabipinol)

II. STRUCTURE-ACTIVITY RELATIONSHIPS

Various synthetic cannabinoids have been tested in animals and appear to produce behavioural effects of the type associated with Δ^8 - and Δ^9 -THC. The major contribution to our knowledge of structure-activity relationships in the THC series is due to Mechoulam and his colleagues (Mechoulam, 1970; Edery, Grunfeld, Porath, Ben-Zvi, Shani, and Mechoulam, 1972). Among other compounds, these workers prepared homologues of Δ^8 - and Δ^9 -THC and tested them in rhesus monkeys for behavioural and somatic effects. Detailed results are given in the original paper, but some of the results for the more active compounds are given in Table 5.2. The main conclusions from these studies were:

1. The tricyclic ring system is a requirement for biological activity.

2. Substitution of a hydrogen on the aromatic ring of Δ^8 - or Δ^9 -THC with a carboxyl, a carbomethoxyl, an acetyl, or an acetoxyl group abolishes or drastically reduces activity.

3. Alkyl substitution at C-2 in the aromatic ring of the THC's (see 5.5) leads to compounds with reduced, but still appreciable, activity. Substitution at C-4, on the other hand, leads to complete loss of activity.

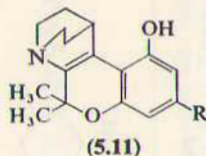
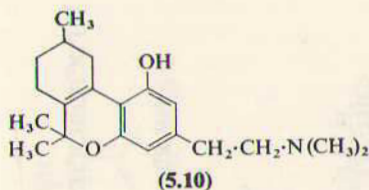
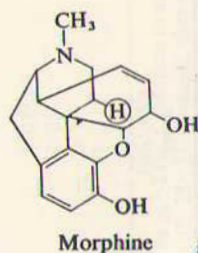
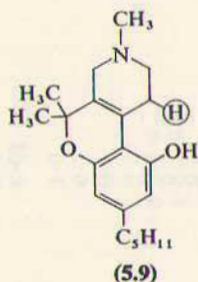
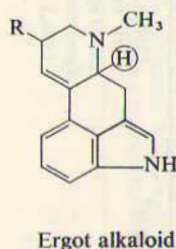
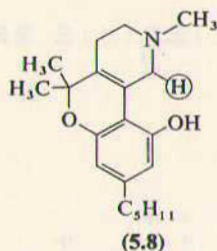
4. Acetylation at C-1 of either Δ^8 - or Δ^9 -THC leads to active compounds.

5. The most active compounds studied, listed in Table 5.2, were those in which modifications were made to the alkyl side-chain of the THC's, emphasizing the necessity for an intact tricyclic system.

Particularly potent compounds are listed in Table 5.2 as *D*, *H*, and *I*, which on a weight-for-weight basis were certainly more active than Δ^8 -THC and probably more active than Δ^9 -THC; their effects were also much more prolonged. Compound *D* was also administered to dogs, which, after a dose of 100 $\mu\text{g./kg.}$ showed increased motor activity that became aimless and compulsory. Later, ataxia developed and later still (about 2 hours after injection) the animals alternated between periods of deep sleep and periods of non-stop running. This phase lasted for about 24 hours, but the ataxia lasted for up to 3 days. A dose of 40 $\mu\text{g./kg.}$ produced hyperactivity and ataxia alternating with periods of sleep, this state lasting for about 5 hours. A dose of 10 $\mu\text{g./kg.}$ had no apparent effect. The authors remark on the species specificity of the tetrahydrocannabinols, since Δ^9 -THC is more potent in monkeys than it

is in dogs, whereas the reverse is true with compound *D* of Table 5.2. A recent study of structure-activity relationships in the $\Delta^{6a,10a}$ -THC series suggests that the 3-(1,1-dimethylheptyl) derivative is twice as potent as the isomeric 3-(1,2-dimethylheptyl) compound (Loev, Bender, Dowalo, Macko, and Fowler, 1973). It will be interesting to see whether the same difference holds in the Δ^8 - and Δ^9 -THC series.

Some alkaloidal analogues of THC's have also been investigated by Pars and Razdan (1971). In designing these nitrogen analogues the

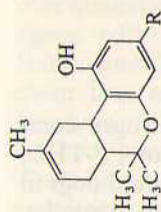


authors considered three factors: phenylethylamine orientation which is found in a large number of antidepressant and analgesic drugs; the aryl piperidine moiety which is present in many CNS active drugs; and the aryl tetrahydropyridine moiety which is found in some newer analgesic drugs, notably spiroperidol and droperidol. They also found some additional points of similarity in the structures



Table 5.2.—ACTIVITY OF Δ^8 - and Δ^9 -TETRAHYDROCANNABINOL ON RHESUS MONKEYS COMPARED TO THE PARENT COMPOUNDS (after Ederly and others, 1972)

Compound	Dose (mg./kg.)	Activity*	Approx. Time to Onset of Symptoms (min.)	Approx. Time for Recovery (hours)
A. $R = C_5H_{11}$ (Δ^9 -THC)	0.05	+	15	1
	0.1	++	10	3
	0.25	+++	10	3.5
	0.5	+++	5	4.5
	0.05	—	—	—
B. $R = C_6H_{13}$	0.1	+	10	5
	0.5	++	5	7
	0.1	—	—	—
C. $R = CH(CH_3)C_4H_9$	0.5	—	—	—
	1.0	++	10	4
	0.05	±	20	2
D. $R = CH(CH_3)CH(CH_3)C_5H_{11}$	0.1	+	20	4
	0.5	++	15	24



E. R = C₃H₁₁ (Δ^8 -THC)

F. R = C₆H₁₃

G. R = CH(CH₃)C₄H₉

H. R = CH(CH₃)CH(CH₃)C₃H₇

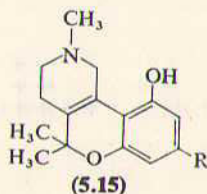
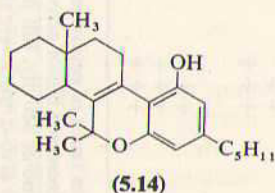
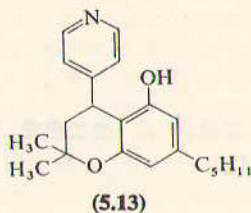
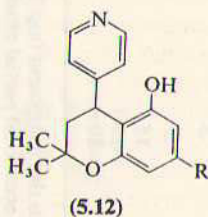
I. R = CH(CH₃)CH(CH₃)C₃H₁₁

0.1	±	15	1
0.25	+	15	1
0.5-0.9	++	10	3
1.0-2.0	+++	10	4
0.05	+	15	1
0.1	++	10	2
0.1	-	-	-
0.2	+	10	6
1.0	+++	3	8
0.025	-	-	-
0.05	++	15	4
1.0	+++	5	30
0.025	-	-	-
0.05	+	15	2
0.1	+++	15	7
1.0	+++	10	48

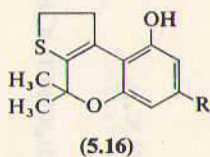
*Activity was rated with reference to Δ^8 -THC; notation in terms of equivalence to this compound (mg./kg., i.v.) are: - No change; $\pm$ (0.1), Tranquility; + (0.25), Drowsiness, decreased motor activity, occasional partial ptosis, occasional head drop; ++ (0.5-0.9), Stupor, ataxia, suppression of motor activity, full ptosis, typical crouched posture, normal behaviour for short periods if external stimuli applied; +++ (1.0-2.0), Severe stupor and ataxia, full ptosis, immobility, crouched posture lasting for more than 3 hours and absence of reaction to external stimuli.

of morphine and the ergot alkaloids. Accordingly, derivatives of structures 5.8 and 5.9 were synthesized, and they (5.10–5.16) are listed (R in all cases is $\cdot\text{CH}[\text{CH}_3]\cdot\text{CH}[\text{CH}_3]\cdot\text{C}_5\text{H}_{11}$).

All the compounds, with the exception of the steroidal analogue (5.14), produced significant central effects when given intravenously



to unanaesthetized dogs. Characteristically, the animals stood in a trance-like state weaving from side to side, pitching forward and backward and overreacting to a swinging object. When aroused the animals showed ataxia for at least 3–4 hours after injection. The most potent compounds were 5.15 and 5.16, which showed effects at doses between 0.2 and 0.5 mg./kg.; the sulphur analogue (5.16)



appeared to give more pronounced effects than the nitrogen compound (5.15). Neither of these compounds, unlike Δ^8 - or Δ^9 -THC, had significant effects on the blood-pressure of anaesthetized dogs in doses ranging from 0.1 to 3.0 mg./kg. Both compounds at 10 mg./kg. decreased spontaneous activity and produced analgesic effects in mice.

III. ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

1. THE FATE OF CANNABIS *IN VIVO*

There has been considerable debate as to the nature of the constituents of the smoke which is inhaled by cannabis users. Smoking machines have been used, and in a study in 1964 Miras, Simon, and Kibunis compared by column and thin-layer chromatography the sublimate obtained from such a machine with an extract of cannabis. Cannabidiol, while being present in the extract, was absent from the sublimate, while the content of THC's was comparable in both samples. The composition of a sublimate prepared by heating a dried extract of hashish to 600°C. under nitrogen differed from the composition of smoke from a marihuana cigarette (Vieira, Aguiar, Alencar, Seabra, Tursch, and LeClerq, 1967). These somewhat contradictory results are possibly a result of the many and varied ways in which cannabis is smoked by different users, leading to different rates of decomposition of the constituents.

More recently, studies at the Battelle Memorial Institute in Columbus, Ohio, have been made using a smoking machine which is programmed to simulate the smoking characteristics of a large number of experienced smokers. The findings of these studies are summarized by Truitt (1971). In general, they have shown, in contrast to some earlier findings, that the ratios of cannabinoids present in smoke are very similar to those present in the plant. One exception to this is that most of the THC-acid precursors are converted by the heat of combustion into THC's. There seems to be little conversion of cannabidiol to THC by ring closure. Perhaps most surprising, in view of the earlier claims by Lerner and Zeffert (1968) and Hively and his colleagues (1966), is that little isomerization of Δ^9 - to Δ^8 -THC seems to occur. Of all the Δ^9 -THC in a cigarette, approximately 50 per cent is found in the smoke or in the butt, and so is theoretically available for absorption into the body. This finding agrees with that of other workers (Manno, Kiplinger, Bennett, Haire, and Forney, 1970), although Claussen and Korte (1968) claim that more than 90 per cent of the THC is destroyed by pyrolysis.

There have been many attempts to detect THC in body fluids. The material is present in only very small amounts and it has been necessary to use chromatography, mass spectrometry, nuclear magnetic resonance, or radioactive techniques. The main problem is that THC is rapidly metabolized *in vivo* in some species; thus,

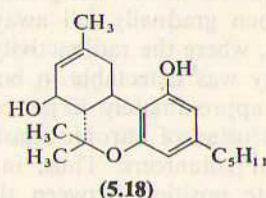
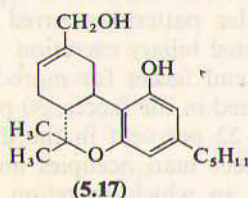
its half-life is about 14 minutes in rabbits (Agurell, Nilsson, Ohlsson, and Sandberg, 1970) and 30 minutes in the rat (Klausner and Dingell, 1971), but apparently much longer in man where a half-life of 56 hours is normal (Lemberger, Silberstein, Axelrod, and Kopin, 1970).

One of the first distribution studies of THC *in vivo* was by Miras (1965), who grew cannabis plants in ^{14}C and then extracted from them ^{14}C -labelled THC. When injected intraperitoneally to rats it was found to be poorly absorbed, with most of the absorbed material being concentrated in the liver. Since then there have been several studies with tritiated material. Most of these are subject to the criticism that total radioactivity in the tissues has been measured, which, since it is known that THC is rapidly metabolized, means that the values represent THC plus metabolites, with the latter probably being predominant.

Agurell and his colleagues (Agurell, Nilsson, Ohlsson, and Sandberg, 1969) treated a purified extract of cannabis with tritiated water and thus obtained a mixture of 97 per cent $\Delta^9\text{-THC-}^3\text{H}$ and 3 per cent cannabinol- ^3H . After intravenous injection of 1.3–3 mg./kg. of this preparation, rats eliminated less than 50 per cent of the radioactivity during the first week. In all, 80 per cent of the material was eliminated in the faeces in metabolized form with the remainder being excreted in the urine, also in metabolized form. If any unchanged $\Delta^9\text{-THC}$ was excreted in the urine it represented less than 0.006 per cent of the injected drug. No glucuronide-bound $\Delta^9\text{-THC}$ was found despite a report by Christensen and Rafaelson (1969) that β -glucuronidase liberated THC metabolites in the urine of human subjects who had received 750 mg. of cannabis resin by mouth. A recent distribution study in rats (Shannon and Fried, 1972) shows that only 0.8 per cent of intraperitoneally administered $\Delta^9\text{-THC}$ is responsible for the changes in the E.E.G. and presumably in behaviour, while less than 0.2 per cent became lipophilically bound in the brain. The drug appears to localize primarily in grey matter and is also deposited extensively in the extrapyramidal areas and the limbic structures. Similar results are apparent in the mouse (Ryrfeldt, Ramsay, Nilsson, Widman, and Agurell, 1973).

Tritiated $\Delta^8\text{-THC}$ was used by Burstein's group (Burstein, Menezes, Williamson, and Mechoulam, 1970). Injection of this drug into rabbits led to urine excretion of several water-soluble tritiated substances, which were assumed to be conjugates of the metabolites of THC. Mass spectrometric examination strongly suggested the presence of 11-hydroxy- $\Delta^8\text{-THC}$ (5.17), although it was possible that the compound was hydroxylated in the 7-position (5.18). Strong evidence for the formation of the 11-hydroxy compounds was

provided in the rat (Foltz, Fentiman, Leighty, Walter, Drewes, Schwarz, Page, and Truitt, 1970). These workers injected tritiated Δ^8 -THC and then examined homogenates of the livers using thin-layer chromatography. Several metabolites were found, and subsequent experiments with ^{14}C -labelled material established that



13 per cent of the injected radioactivity was found in the liver 30 minutes after injection. Of this, 60 per cent was the major metabolite, having the same R_F value as a metabolite formed *in vitro* when Δ^8 -THC was incubated with rat liver microsomal preparations and which had been positively identified as 11-hydroxy-*trans*- Δ^8 -THC.

Three major metabolites were found in the urine of rabbits injected with ^{14}C -labelled Δ^9 -THC (Nilsson, Agurell, Nilsson, Ohlsson, Sandberg, and Wahlqvist, 1970). When the compound was incubated with the supernatant from a homogenate of rabbit liver, a phenolic compound, identified as 11-hydroxy-*trans*- Δ^9 -THC, contained about 95 per cent of the total radioactivity. It was stated that this metabolite was pharmacologically active in mice. A similar report by Wall, Brine, Brine, Pitt, Freudenthal, and Christensen (1970) followed incubation of synthetic Δ^9 -THC with rabbit liver homogenates; two separate metabolites were found, one of which was about as active as Δ^9 -THC while the other possessed no detectable biological activity.

That 11-hydroxylation of THC also occurs in man seems to be shown by the work of Lemberger and his colleagues (Lemberger and others, 1970; Lemberger, Axelrod, and Kopin, 1971). Normal volunteers with no history of previous exposure to cannabis were injected intravenously with 0.5 mg. of ^{14}C -labelled Δ^9 -THC. Blood samples were taken at intervals after the injection and analysed for Δ^9 -THC, total radioactivity, and ether-extractable radioactivity. Plasma levels of all three fell rapidly in the first few hours after injection but thereafter much more slowly. Δ^9 -THC could be detected in plasma for at least 3 days, as could total and ether-extractable radioactivity, presumably representing metabolites. The presence of 11-hydroxy- Δ^9 -THC in the plasma was confirmed by chromatography. Similar studies were also carried out on habitual

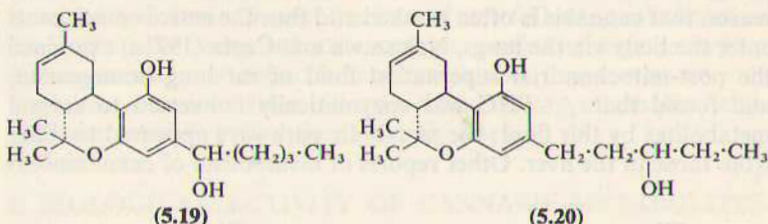
smokers of marihuana, the most significant finding being that Δ^9 -THC had a shorter plasma half-life in these subjects than in the normal volunteers.

In all subjects Δ^9 -THC was metabolized to more polar compounds, which were excreted in urine and faeces. Radioactivity levels in the urine were greatest in the first 24 hours after injection, but then gradually fell away. A similar pattern occurred in the faeces, where the radioactivity represented biliary excretion. Radioactivity was detectable in both urine and faeces for more than 7 days; approximately 40 per cent appeared in the faeces, 30 per cent in the urine of chronic smokers, and 22 per cent in the urine of normal volunteers. Thus, in this respect man occupies an intermediate position between the rabbit, in which excretion occurs mainly in the urine (Agurell and others, 1970), and the rat, where faecal excretion is more important (Agurell and others, 1969). Virtually no unchanged Δ^9 -THC appeared in the urine of human subjects and only small amounts of 11-hydroxy- Δ^9 -THC, although amounts of the latter could be increased somewhat by enzymatic hydrolysis with β -glucuronidase. The major fraction of urinary radioactivity, however, consisted of more polar compounds. In faeces, 11-hydroxy- Δ^9 -THC accounted for up to 20 per cent of the total radioactivity.

Since the effects of smoking marihuana seem to be maximal within 15 minutes, much less after 30 to 40 minutes, and largely absent after 3 hours (Weil, Zinberg, and Nelsen, 1968; Jones and Stone, 1970), the occurrence and disappearance of 11-hydroxy-THC in the plasma at times roughly corresponding to these seems to lend weight to the view that it is an active metabolite. Nevertheless, while 11-hydroxy- Δ^9 -THC may be the major metabolite in man, it is certainly not the only one. Wall and his colleagues reported the allylic oxidation of Δ^9 -THC to its 11-hydroxy derivative and then to the 8,11-dihydroxy compound, and the former metabolite also undergoes aromatization to the corresponding cannabinol (Widman, Nilsson, Nilsson, Agurell, and Leander, 1971). More recent studies by Wall's group (Wall, Brine, Perez-Reyes, and Lipton, 1971; Wall, Brine, Pitt, and Perez-Reyes, 1972) have demonstrated that Δ^9 -THC is also partially metabolized in man to the isomeric 8α - and 8β -hydroxy- Δ^9 -THCs, both of which appear to exhibit behavioural activity in animals (Ben-Zvi, Mechoulam, Edery, and Porath, 1971). The same group (Pitt, Hauser, Hawks, Sathe, and Wall, 1972) has also described synthetic methods for all the metabolites of Δ^9 -THC, and pharmacological studies are awaited with interest.

Hydroxylation of Δ^8 - and Δ^9 -THC also occurs in the pentyl side-chain, at least in animals. Incubation of ^{14}C -labelled Δ^8 -THC

with the 9000 g. supernatant fraction of male beagle liver allowed isolation of 11-hydroxy- Δ^8 -THC (5.19) and its 3-isomer (5.20) (Maynard, Gurny, Pitcher, and Kierstead, 1971). Administration of Δ^9 -THC to rabbits was followed by urinary excretion of analogous



compounds but also containing carboxyl functions at C-9; the methyl group had clearly undergone oxidation *in vivo*, in addition to the side-chain hydroxylation (Burstin, Rosenfeld, and Wittstruck, 1972). No information is available concerning the possible biological properties of these metabolites, but preliminary work indicates that the processes also occur in man. The production of polar acidic metabolites is a major metabolic route in most species for Δ^8 - and Δ^9 -THC. However, it appears not to be so in the rabbit for the synthetic cannabinoid DMHP, the prolonged half-life of which may be due to it not being cleared by the kidneys as a polar derivative (Lemberger, McMahon, Archer, Matsumoto, and Rowe, 1973).

In the present state of knowledge, 11-hydroxy- Δ^9 -THC remains the only cannabis metabolite with proven psychotropic activity in man, though recent work (Perez-Reyes, Timmons, Lipton, Dix, Davis, and Wall, 1973) suggests that 11-hydroxylation does not alter the potency of Δ^9 -THC while 8 β -hydroxylation reduces it and 8 α -hydroxylation abolishes it. Nevertheless, the extensive microsomal hydroxylation of THC's lends support to the view (Ben-Zvi and others, 1971) that the cumulative effects of smoking cannabis are based upon a number of physiologically active cannabinoids formed during its metabolism. A diagrammatic summary of the human metabolism of Δ^9 -THC is presented in Fig. 5.1. The recent work in this area can be summarized as implying that while Δ^9 -THC is rapidly converted in the liver to its 11-hydroxy derivative, the latter does not pass readily into the blood. Instead it is carried by the bile to the small intestine, is not reabsorbed, and is eventually excreted via the faeces. The metabolism of Δ^9 -THC in man involves initial rapid hydroxylation at C-11, this primary metabolite being in turn rapidly converted to 11-carboxy- Δ^9 -THC. Secondary hydroxylation at C-2' or C-8 occurs more slowly but is substantial, resulting

in a mixture of neutral and acidic metabolites. Thus it is still not clear how much, if any, of these compounds actually reaches the brain, or which, if any, is the pharmacologically active compound.

There is also some question as to whether biotransformation of Δ^9 -THC can occur at sites other than the liver. For the obvious reason that cannabis is often smoked and thus the active constituents enter the body via the lungs, Nakazawa and Costa (1971a) examined the post-mitochondrial supernatant fluid of rat lung homogenates and found that Δ^9 -THC was enzymatically converted to several metabolites by this fluid; the metabolic pathways appeared to differ from those in the liver. Other reports of metabolism of cannabinoids

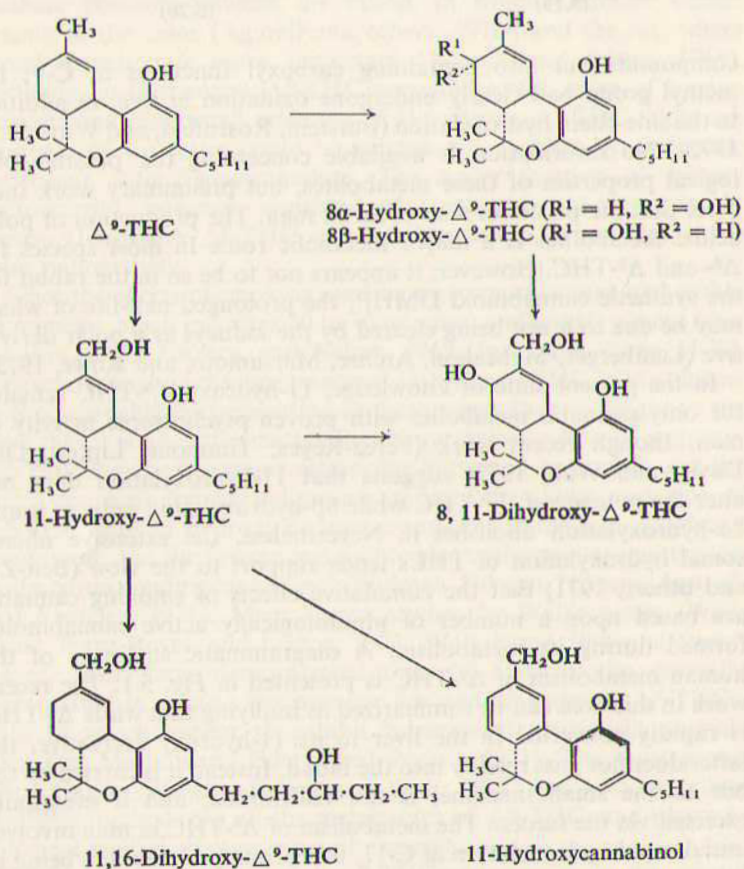


Fig. 5.1.—Biotransformations of Δ^9 -tetrahydrocannabinol in man (mainly in the liver by microsomal non-specific oxidases).

in the lungs, spleen, and blood are available (Christensen, Freudenthal, Gidley, Rosenfeld, Boegli, Testino, Brine, Pitt, and Wall, 1971; Nakazawa and Costa, 1971b), but positive identification of the metabolic pathways has yet to be made for sites other than the liver. Recent work (Leighty, 1973) has shown an increased percentage of hydroxylated metabolites in the liver of rats following inhalation of Δ^9 -THC smoke compared to intravenous injection, together with a high percentage of these metabolites in the lungs even at only 5 minutes after inhalation. Clearly, the lungs can metabolize tetrahydrocannabinols before they reach the liver.

2. BIOLOGICAL ACTIVITY OF CANNABIS METABOLITES

11-Hydroxy- Δ^8 -THC can be produced chemically from Δ^8 -THC with relative ease (Foltz and others, 1970). Such a product, with greater than 90 per cent purity, was studied by Truitt (1970) for its behavioural effect in rats. It produced a pattern of activity very similar to that produced by both Δ^8 - and Δ^9 -THC in that the animals were cataleptic with bizarre behaviour (retropulsion and backward circling), abnormal biting, hyperstartle reactions, decreased spontaneous activity, and vocalization in response to mild stimuli. The time-course of the action of all three drugs was similar and the potency of 11-hydroxy- Δ^8 -THC was equal to or slightly greater than that of Δ^8 - or Δ^9 -THC. Pure 11-hydroxy- Δ^8 -THC, prepared by *de novo* synthesis, is reported to produce similar effects in the monkey (Ben-Zvi, Mechoulam, and Burstein, 1970).

11-Hydroxy- Δ^9 -THC, isolated from liver microsomal preparations incubated with the parent THC, has shown behavioural activity in the mouse comparable to that of Δ^9 -THC (Nilsson, Nilsson, and Agurell, 1969; Wall and others, 1970). It appears to be about 7 times more potent than Δ^9 -THC in producing cataleptic reactions in rodents (Gill, Jones, and Lawrence, 1973) but up to 18 times more potent in the mouse upon intracerebral injection (Christensen and others, 1971). Clearly human studies are necessary in order to settle finally whether this metabolite is responsible for all or most of the central effects of cannabis, and such evidence has recently appeared.

Lemberger, Crabtree, and Rowe (1972) administered tritiated 11-hydroxy- Δ^9 -THC (1 mg., 24 μ C) intravenously to three normal male volunteers. All had smoked marihuana in the past but not in the year prior to the study. Within two minutes signs and symptoms appeared in all subjects. Heart-rates increased by 20–50 beats per minute, returning to normal in 2–5 hours. The subjects also experienced a psychological 'high' which reached a peak between 2 and 3 minutes after drug injection and which was unpleasant in two of

the three subjects; pleasant feelings were reported later, however. Plasma levels of total radioactivity and unchanged tritiated 11-hydroxy- Δ^9 -THC declined rapidly during the first few hours, but after 8 hours the decline was slower and the mean half-lives for total radioactivity and 11-hydroxy- Δ^9 -THC were respectively 40 and 22 hours. By the end of the first day, 16 per cent of the total radioactivity had been excreted in the urine, but only 27 per cent by the end of the week. The original drug accounted for very little of the radioactivity, which was mainly due to an unidentified polar acidic compound. This could be one of the C-9 acids reported to occur in rabbits following administration of Δ^9 -THC (Burstein and others, 1972). About half of the total radioactivity was excreted in the faeces in the week following drug injection. It was mainly in the form of unchanged 11-hydroxy- Δ^9 -THC and its 8,11-dihydroxy analogue. Thus, this dose of about 14 $\mu\text{g./kg.}$ of 11-hydroxy- Δ^9 -THC produced physiological and psychological effects typical of cannabis, and it seems to be an active metabolite in man.

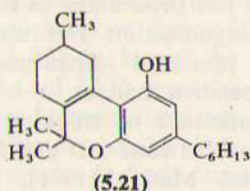
In another study, either Δ^9 -THC or 11-hydroxy- Δ^9 -THC, suspended in 25 per cent human serum albumin, was given by intravenous infusion to volunteer subjects (Perez-Reyes, Timmons, Lipton, Davis, and Wall, 1972). The subjects were instructed to terminate the infusion when they felt that they had arrived at the desired level of 'high'. The doses necessary to achieve this level were 3.10 ± 0.90 mg. of Δ^9 -THC and 2.27 ± 0.81 mg. of the metabolite. There was no significant difference between these doses. The interpretation of these results is not easy; presumably, it is either that Δ^9 -THC is active in its own right or that it is extremely quickly metabolized to the 11-hydroxy compound. Experiments in mice support the latter possibility. Thus, Gill and Jones (1972) injected tritium-labelled Δ^9 -THC into mice and followed brain levels of this substance and of the 11-hydroxy metabolite in the animals. It was found that metabolism of Δ^9 -THC to its 11-hydroxy derivative was fast and that both substances penetrated into the central nervous system. Brain concentrations of either substance showed a good correlation with inhibition of spontaneous motor activity in the mice. The conclusion was that 11-hydroxy- Δ^9 -THC is centrally active, but the evidence did not permit the conclusion that the effects of Δ^9 -THC are due solely to this, its major metabolite.

For the remainder of this Chapter it is reasonable to assume that reference to the effects of THC, or indeed of crude cannabis preparations, may be taken to mean that the effects are probably due to active metabolites, notably 11-hydroxy- Δ^9 -THC. Recent clinical studies (Perez-Reyes, Lipton, Timmons, Wall, Brine, and Davis, 1973) suggest that the biological half-life of Δ^9 -THC is less

than 48 hours, with the major urinary and plasma metabolites being the 11-hydroxy and 8,11-dihydroxy derivatives. Nevertheless, intravenous infusion of 11-hydroxy- Δ^9 -THC did not significantly enhance the effects seen with similar doses of the parent compound, while other monohydroxylated metabolites (8 α - and 8 β -hydroxy- Δ^9 -THC) were very much less potent (Perez-Reyes, Timmons, Lipton, Christensen, Davis, and Wall, 1973).

IV. EFFECTS OF CANNABIS IN MAN

Innumerable accounts have been written of the effects of cannabis in man. Many of these are anecdotal, colourful accounts written by users of the drug. Most suffer from the fact that it is impossible to



assess the amounts of the active principles absorbed, and they are useless in any attempt to correlate dose with effect. That a clear relationship does exist between dose and effect has been pointed out by Isbell (1971), who also lists the most consistent effects which have been observed. Objectively, tachycardia, conjunctival vascular congestion, and increased body sway are reported. Subjective effects include elation, euphoria, sensory perceptual distortion, depersonalization, and hallucinations, although the latter occur only after large doses. Sedation often follows the initial elation. There is also an impairment of the ability to think clearly. The severity of all these effects varies with dose and they occur after administration of the synthetic compounds $\Delta^{6a,10a}$ -5-*n*-hexyl-THC (synhexyl, pyrahexyl, 5.21) or $\Delta^{6a,10a}$ -5-*n*-pentyl-THC (5.4) as well as after Δ^9 -THC, though the latter is more potent. The effects of crude cannabis preparations seem to be proportional to their content of Δ^9 -THC.

A more detailed review of the relationship between the dose of cannabis and the response by human subjects was carried out by Kiplinger and Manno (1971). They note that, as for studies in animals, human studies carried out before 1966 are unreliable because of confusion concerning the identity and concentration of the pharmacologically active principle in crude drug preparations.

Perhaps some of the more interesting studies are those in which the effects of the drug when ingested have been compared with those when it is smoked. One such was by Isbell and others (1967), in which doses of 50 or 200 $\mu\text{g./kg.}$ of $\Delta^9\text{-THC}$ were given to volunteers in cigarettes and the effect compared with that of 120 or 480 $\mu\text{g./kg.}$ given by mouth. There were clear dose-effect relationships on both pulse-rate and subjective responses. Using pulse-rate as the response, the drug was 2.6 times more potent when smoked than when ingested, but this figure is probably low because only about 50 per cent of the available drug in a cigarette seems to be inhaled; it is likely that the drug is about 5-6 times more potent by smoking than by mouth.

The effects on normal volunteers of multiple doses of standardized cannabis extracts containing 0, 20, 40, or 60 mg. of $\Delta^9\text{-THC}$, given by mouth, were studied by Melges and his colleagues (1970). They used four psychological test procedures to evaluate recent memory function and temporal organization. The results seemed to indicate clearly that the drug produced impairment of recent memory formation in a dose-dependent manner.

The effects on performance of smoking marihuana cigarettes giving 'delivered doses' of between 6.25 and 50 $\mu\text{g./kg.}$ were investigated by Kiplinger and Manno (1971). In these experiments measurements were made of pulse-rate, subjective effects, motor performance, and verbal performance. Clear dose-response relationships were apparent for pulse-rate and for subjective effects, but they were rather less clear for the other measured parameters. Alcohol had an additive effect with cannabis.

Other studies designed to demonstrate dose-response relationships have been summarized by Kiplinger and Manno (1971). The general conclusion is that the effects of cannabis, its active constituents, or its analogues, in man are related to the dose. This is clearly the case for the tachycardia, but also applies to various measurements of psychomotor performance, replies to questionnaires, mental performance, and short-term memory. Hallucinatory and psychotic manifestations of the action of the drug also appear to be dose-related but appear only at dose levels much higher than those which produce the characteristic euphoric effects of cannabis.

Hollister (1971) reported other studies on man in which the effects of $\Delta^9\text{-THC}$ were compared with those of $\Delta^{6a,10a}\text{-THC}$ (5.4) and those of the semi-synthetic compound synhexyl (5.21). In the first series of experiments oral doses of 10-70 mg. of $\Delta^9\text{-THC}$ and 50-150 mg. of synhexyl were used. The drugs produced similar clinical effects with synhexyl being rather less potent but having a slower onset and longer duration of action than $\Delta^9\text{-THC}$. The latter

finding may reflect a slower rate of biotransformation of synhexyl to an active metabolite. In view of the finding (Isbell and others, 1967) that $\Delta^{6a,10a}$ -THC was relatively inactive by smoking, Hollister's second series of experiments were designed to compare the effects of the compound with those of Δ^9 -THC and synhexyl when administered by smoking. The amount of Δ^9 -THC contained in each cigarette was 12 mg., with 15 mg. of the other two compounds being used. The conclusion from this study was that Δ^9 -THC is about 3-6 times more potent than either synhexyl or $\Delta^{6a,10a}$ -THC, with the effects of the latter two compounds being less intense and of shorter duration. If this estimate of the activity of $\Delta^{6a,10a}$ -THC is correct, then it removes some of the objections to the use of the material as a standard in biological experiments prior to 1965, when it was assumed to be the biologically active constituent of cannabis.

There have been some comparisons made of the effects of Δ^9 -THC with those of other psychoactive drugs. Isbell and Jasinski (1969) compared doses of 75-225 $\mu\text{g./kg.}$ of the cannabis principle with those of 0.5-1.5 $\mu\text{g./kg.}$ of LSD given by intramuscular injection. Subjectively, differences between the drugs were not easy to detect, but there were clear differences in the physiological effects produced. Thus, LSD caused increases in body temperature, blood-pressure, and deep tendon reflexes, together with mydriasis. Δ^9 -THC produced none of these. Hollister and Gillespie (1969) came to essentially the same conclusion, although they felt that Δ^9 -THC produced less total impairment of function with more euphoria and dream-like states than LSD.

Hollister and Gillespie (1970) also compared the effects of oral doses of 0.5 mg./kg. of Δ^9 -THC (as marihuana extract) with those of 950 mg./kg. of ethanol and 0.2 mg./kg. of dextroamphetamine. While ethanol and Δ^9 -THC reduced activity, dextroamphetamine made the subjects more active and less drowsy. Similarly, both Δ^9 -THC and ethanol impaired performance in psychometric tests but the amphetamine enhanced it. These and other experiments suggest that marihuana does not produce stimulation followed by sedation but that it gives a general sedation similar to that of ethanol. In another comparative study of cannabis and ethanol, Jones and Stone (1970) gave 950 mg./kg. of ethanol by mouth and marihuana either by smoking (dose equivalent to 9 mg. of Δ^9 -THC) or by mouth (dose equivalent to 90 mg. Δ^9 -THC). The subjects in this trial were all habitual heavy users of marihuana and the findings were somewhat remarkable. Neither the large dose of ethanol nor that of marihuana by smoking had any appreciable effect, suggesting that the subjects had become tolerant to marihuana and had

developed cross-tolerance to ethanol. The oral dose of marihuana could be detected by the subjects given it blind, indicating that 90 mg. of Δ^9 -THC by mouth is more effective than one-tenth of that dose given by smoking.

The evidence relating to the effects of cannabis on the electroencephalogram (E.E.G.) in man is somewhat conflicting. There were several early reports of decreases in alpha activity (7.5–13.5 Hz) accompanied by increases in beta (18.5–25.4 Hz) and theta (3.5–7.5 Hz) activity (Wikler and Lloyd, 1945; Williams, Himmelsbach, Wikler, Ruble, and Lloyd, 1946; Ames, 1958). More recently, Rodin, Domino, and Porzak (1970) reported a shift in the centre frequency of the E.E.G. from 11 to 9–10 Hz in volunteers who smoked marihuana. However, Jones and Stone (1970) failed to find consistent changes in the E.E.G.s of volunteers who were given either marihuana or Δ^9 -THC by mouth. Volavka, Dornbush, Feldstein, Clare, Zaks, Fink, and Freedman (1971) reported two studies; in the first, 4 subjects were given two marihuana cigarettes daily, each containing 6.5 mg. of Δ^9 -THC. Initially, post-smoking euphoria was common but dysphoria appeared during the third to sixth days. This became so pronounced in 2 of the subjects that they withdrew from the experiment on days 10 and 11 respectively. The other 2 subjects completed the planned 22-day schedule. The effect on the E.E.G. can be summarized as producing synchronization, that is an increase in the amplitude and a decrease in the frequency. The behavioural effects disappeared within 5 days of the last drug administration, the E.E.G. effect somewhat sooner. The second study was an acute one in which marihuana cigarettes containing either 7.5 or 22.5 mg. of Δ^9 -THC were smoked over a period of 12–38 minutes. There was an E.E.G. effect of rapid onset and short duration, consisting of increases in per cent time alpha and an associated decrease in theta and beta bands. Tests were also made of the performance of the subjects in short-term memory and reaction-time tasks, with a dose-dependent impairment in both.

From 1968 to 1971 there were no studies in the United States involving the administration of pure Δ^9 -THC to man. The Food and Drug Administration ruled that the drug should be subjected to the same types of toxicological investigations as are appropriate to medicinal substances. Clearance has now been given and work has resumed at a renewed pace. Two recent studies with Δ^8 - and Δ^9 -THC show that the ratio of potencies is about 2 : 3 either when given intravenously as ethanolic solutions or by mouth (Hollister and Gillespie, 1973; Hosko, Kochar, and Wang, 1973). Both compounds increased pulse-rate, altered subjective feelings, caused hyperreflexia,

and upset postural responses in the absence of visual cues. Some subjects also exhibited lowered oral temperature, changes in visual evoked responses, and alteration of sleep patterns. The major psychic changes were mental lethargy and confusion and spontaneous hilarity. Maximal effects were observed within 3-4 minutes following an intravenous dose of 6 mg. of Δ^9 -THC or after 30-90 minutes following oral doses of 40 mg. of Δ^8 -THC; effects lasted for up to 5½ hours. The speed and degree of oral absorption was very dependent both upon the vehicle used and the individual subject, which may explain some of the variations in clinical experiences (Perez-Reyes and others, 1973).

V. EFFECTS OF CANNABIS IN ANIMALS

There have been many reports on the toxicology, pharmacology, and biochemistry of cannabis. Many of them suffer from the usual criticism that crude extracts with variable content of active principle were used. In recent years, increasing numbers of studies have been carried out using Δ^8 -THC and Δ^9 -THC, and emphasis will be placed on these. Certain aspects of the pharmacology and biochemistry of the drug are also referred to in Chapter 8, where its mode of action is discussed.

Gill and Paton (1970) drew attention to the fact that the general pharmacology of cannabis suggests analogies with various centrally acting drugs. Thus, the euphoria and certain sympathomimetic actions are reminiscent of cocaine and amphetamine; the euphoria and analgesia of morphine; the sensory disturbances of LSD; the tachycardia of atropine or hyoscine. There is also a general resemblance to the effects of alcohol. The structure of Δ^9 -THC, with its phenolic hydroxyl group, shows certain similarities to the structures of morphine and the catecholamines. In view of these considerations, Gill and Paton chose to study the effects of various preparations of cannabis *in vitro* on two isolated smooth-muscle preparations, the guinea-pig vas deferens and the guinea-pig ileum, both excited by field stimulation. Petrol-soluble and insoluble fractions of Tincture of Cannabis B.P.C. were used, the insoluble fraction being further fractionated by column chromatography and counter-current distribution. One fraction had an infra-red spectrum identical to that of Δ^8 -THC. The results indicated that at least three active principles were present. These were provisionally compared with atropine, an alcohol, and with morphine or cocaine. It was emphasized that the comparisons were operational, not necessarily indicating identical mechanisms of action with these standard drugs.

1. TOXICOLOGICAL STUDIES

The acute toxicity of pure Δ^9 -THC to rats and mice by various routes of administration has been studied in two media, 10 per cent Tween 80 (Phillips, Brown, Martz, Hubbard, and Forney, 1971) and albumin suspensions (Harris, 1971). The results are summarized in Table 5.3, together with Harris's results for Δ^8 -THC. They indicate that the albumin suspensions were usually less toxic than Tween solutions, presumably indicating that the latter were better absorbed. Phillips, Brown, and others, reported that death occurred with

Table 5.3.—ACUTE TOXICITY OF Δ^9 - AND Δ^8 -THC

SPECIES	ROUTE OF ADMINISTRATION	<i>LD₅₀ (mg./kg.)</i>		
		Δ^9 -THC		Δ^8 -THC
		Phillips, Brown, and others (1971)*	Harris (1971)†	Harris (1971)†
Mouse	Intravenous	42.5	60	31
	Intraperitoneal	455	168	210
	Intragastric	482	1900	> 2000
Rat	Intravenous	28.6	100	97
	Intraperitoneal	373	430	560
	Intragastric	666	> 2000	> 2000

*Solutions in 10 per cent Tween 80.

†Suspension in albumin.

respiratory depression and that the only post-mortem finding of note was congestion and oedema of the lungs.

In a subacute study, Phillips, Turk, and Forney (1971) gave Δ^9 -THC suspensions by intraperitoneal injection daily to rats for 30 days. Doses of up to 30 mg./kg. were used. The main effect observed was that the animals became hypersensitive to external stimuli after the injection but then showed ataxia, lacrimation, diarrhoea, and depression. There were no indications of tolerance to the drug; on the contrary, the animals appeared to become more sensitive to its effects.

Some studies have also been made of the effects of cannabis on the foetus. Persuad and Ellington (1967) gave a single intraperitoneal dose of 16 mg./kg. of cannabis resin to pregnant mice on day 6 of the gestation period. No foetal abnormalities or reductions in the

size of litter were observed, but there was stated to be a high incidence of overall stunting of the foetuses. In animals given 16 mg./kg. of the resin daily during days 1-6 of gestation, there was complete foetal resorption. In a later study, Persuad and Ellington (1968) used rats which were given cannabis resin as a suspension in 1 per cent Tween 80. Pregnant females were given 4.2 mg./kg. of the suspension daily by intraperitoneal injection on days 1-6 of gestation. In these animals, 57 per cent of the foetuses were malformed whereas there were no malformations in a corresponding control group. There are also two reports by Geber and Schramm (1969a, b) of foetal abnormalities occurring in hamsters given marihuana extract (s.c., 25-300 mg./kg.) during the gestation period.

More recently, Pace, Davis, and Borgen (1971) have made a thorough study of the effects of Δ^8 - and Δ^9 -THC given to rats, hamsters, and rabbits prior to and during gestation. The effects of Δ^9 -THC on chromosomes and the transfer of ^{14}C -labelled material across the placental barrier were also investigated. In the first experiments, subcutaneous doses of Δ^9 -THC ranging from 0.01 to 100 mg./kg. were given daily to pregnant rats during the first 20 days of gestation. The offspring showed small subdermal haemorrhages about the head and shoulders at birth which disappeared within a few days, and were otherwise normal. Only in the 100 mg./kg. group was there any reduction in litter size (a mean of 7.8 compared to the control figure of 10.4). There was a high incidence of neonatal deaths, especially in the higher dose groups, which seemed to be due to inadequate milk production by the mothers. In another experiment, Δ^8 - or Δ^9 -THC in doses of up to 40 mg./kg. were administered every other day to female rats for a period of 30 days prior to conception and every day for 20 days of the gestation period. Except for bruising about the head and shoulders there were no abnormalities in the offspring of these animals, and when they mated to produce the next generation again there were no defects. All groups did, however, show a high mortality rate.

Doses as high as 200 mg./kg. given daily throughout the gestation period failed to produce foetal abnormalities, although some of the maternal organs were affected. In particular, there were increases in the weights of adrenals, thyroids, and hearts, possibly reflecting the pituitary-adrenal activation previously reported for Δ^9 -THC by Dewey and his co-workers (Dewey, Harris, Howes, Granchelli, Pars, and Razdan, 1970; Dewey, Peng, and Harris, 1970) and Kubena, Perhach, and Barry (1971). Increases in liver weight were also noted, suggesting possible hepatotoxic effects of repeated THC-administration. In another study using hamsters, a marihuana extract containing 17.1 per cent Δ^9 -THC was used. Pregnant

animals received 200–300 mg./kg. of the extract on days 6, 7, and 8 of gestation, the period of major organogenesis. The animals were either sacrificed on day 14 or allowed to go to term. No foetal abnormalities or changes in litter number or weight were found. Similarly, no abnormalities were found in the progeny of animals exposed to smoke containing Δ^9 -THC during gestation.

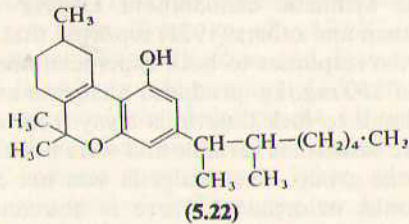
In the chromosome studies, 25 mg./kg. of Δ^9 -THC was given for a total of 50 days to female rats. No breaks were observed in the leucocyte chromosomes of these animals. Only limited amounts of ^{14}C -labelled Δ^9 -THC were able to pass the placental barrier, when it was given to pregnant rats, and this may explain the apparent innocuousness of the substance to the foetus.

It is apparent that there is contradictory evidence concerning the possible teratogenicity of Δ^9 -THC, or more particularly of cannabis extract. It is possible that the latter contains a teratogen which is not THC, but further studies are clearly required. This also applies to the assessment of possible adverse behavioural effects in man, which have been claimed to occur after marihuana smoking. Usually little information is available concerning the precise nature of the cannabis preparation, the dose, the circumstances in which it was taken, or the psychiatric state of the user, and most of the reports lack scientific objectivity. Possibly the best review of this subject is by Murphy (1965), who noted the contradictions and confusions in the literature and concluded that there was little evidence for a higher incidence of psychoses among users of cannabis than among the general population. More recent reports do little to invalidate this conclusion.

Nevertheless, there is evidence that materials commonly added to cannabis, or adulterants which are present in the natural material, may give rise to bizarre and serious behavioural disturbances. *Datura stramonium*, the Jamestown or Jimson weed, a solanaceous plant which contains appreciable quantities of hallucinogenic atropine-like drugs (see Chapter 6), is commonly added to marihuana, especially in South America and the South-eastern United States (Walton, 1938). Other solanaceous plants seem to be used similarly (Krantz and Carr, 1969), and it is likely that a wide variety of hallucinogenic agents have been used in combination with cannabis. These may be, at least in part, responsible for so-called 'marihuana psychosis', as, for example, reported in U.S. soldiers in Vietnam (Talbot and Teague, 1969). Certainly, a comprehensive study of a U.S. Army population of 36,000 soldiers concluded that toxic psychoses were rare occurrences except when cannabis was taken simultaneously with alcohol or other psychoactive drugs (Tennant and Groesbeck, 1972).

2. PHARMACOLOGICAL STUDIES

The central effects of cannabis are clearly of greater relevance to its hallucinogenic activity than are those in the peripheral nervous system; many of the latter will not, therefore, be mentioned except where they illustrate structure-activity relationships or other interesting features of cannabis pharmacology.



Effects on the cardiovascular system were summarized by Hardman, Domino, and Seevers (1971). It is clear that synthetic THC derivatives with a double bond in the 6a,10a position produce marked hypotensive effects in dogs, cats, monkeys, and man. The most potent compound in this respect appears to be 1-hydroxy-3-(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran (5.22; dimethylheptylpyran; DMHP). Doses of 1 mg./kg. given to anesthetized dogs produce a mean fall in blood-pressure of 72 mm. Hg. The threshold dose to produce hypotension was about 0.05 mg./kg. Hardman and his colleagues explored the mechanism of action of DMHP in producing this effect, and concluded that it was brought about in part by a decreased sympathetic tone to peripheral blood-vessels. The compound also appeared to have a central action in depressing medullary vasomotor sites.

The evidence relating to the naturally-occurring Δ^9 - and Δ^8 -THCs is not so clear. Boyd and his co-workers (Boyd, Boyd, and Brown, 1971; Boyd, Boyd, Muchmore, and Brown, 1971) reported that both substances given intravenously to squirrel monkeys caused marked effects due to falls in arterial blood-pressure. However, Isbell's group (Isbell and others, 1967; Isbell and Jasinski, 1969) reported no change in blood-pressure when Δ^9 -THC was administered to man. Low doses of Δ^8 - and Δ^9 -THC (0.1-0.3 mg./kg.) potentiate the cardiovascular effects of adrenaline and nor-adrenaline in the anaesthetized dog (Dewey, Harris, and others, 1970; Dewey, Peng, and Harris, 1970).

There have been various reports of the analgesic effects of the THCs (Bicher and Mechoulam, 1968; Buxbaum, Sanders-Bush, and Efron, 1969; Buxbaum, 1972), but the results are very variable and

depend upon the species, the solvent used, the route of administration, and the method of testing (Harris, 1971). While it is clear that cannabis derivatives have some analgesic activity their profiles of activity are different from those of analgesics in clinical use. Chesher, Dahl, Everingham, Jackson, Marchant-Williams, and Starmer (1973) concluded that although cannabis and the narcotics share several common pharmacological properties, their modes of action are distinct. The synthetic cannabinoid DMHP also has such properties. Hardman and others (1971) reported that 1 mg./kg. (i.v.) in dogs blocked the responses to both superficial and deep pain. In rats, oral doses of 150 mg./kg. produced analgesia as judged by the failure of the animals to flick their tails away from a hot wire, but the responses were somewhat variable and were not shown by all the animals in any one group. The analgesia was not reversed by the morphine antagonist nalorphine. There is abundant evidence to show that cannabinoids produce a marked hypothermia in experimental animals. The first report of this was made by Hardman, Domino, and Seevers (1957), who showed that 1 mg./kg. of DMHP given intravenously to dogs produced a significant reduction in rectal temperature which persisted for at least 24 hours. The effect appeared within 2 hours of administration of the drug. Later, Miras (1965) showed that intraperitoneal doses of 100–500 mg./kg. of cannabis resin extract, containing about 0.25 mg. of THC per 100 mg. of extract, produced hypothermia in rats, as did the synthetic THC's. Again the effects were long-lasting. Similar results were reported by Garattini (1965), who also found that intracerebral injections of an extract of hashish produced a hypothermic response. That mice are also susceptible in this respect was demonstrated by Holtzman, Lovel, Jaffe, and Freedman (1969), using Δ^9 -THC. Thus, hypothermia was produced by doses in excess of 1 mg./kg., and the effect, both in degree and duration, was dose-dependent; a dose of 200 mg./kg. gave hypothermia lasting for at least 24 hours. Holtzman and others (1969) reported a finding of particular significance, in that the hypothermia coincided with increased concentrations of noradrenaline and 5-hydroxytryptamine in the brain. It should be noted, however, that other workers have been unable to confirm these changes in amine concentrations (Leonard, 1972), while there also seems to be a dissociation between the behavioural effects of Δ^9 -THC in animals and its effects on the metabolism of brain amines, particularly 5-hydroxytryptamine (Gallagher, Sanders-Bush, and Sulser, 1972). Moreover, Δ^9 -THC seems to cause, at least in rats, a decrease in brain noradrenaline concomitant with any increase in concentrations of 5-hydroxytryptamine (Schildkraut and Efron, 1971). Nevertheless, the work of Feldberg (1966) has shown

that temperature control mechanisms in the hypothalamus may be mediated through the release of catecholamines and 5-hydroxytryptamine. Certainly, intraperitoneal Δ^9 -THC produces circling behaviour in rats, an effect which is potentiated by amphetamine, suggesting that Δ^9 -THC selectively inhibits the release of dopamine within the nigro-striatal neuronal system which controls this behaviour (Waters and Glick, 1973).

Lomax and Campbell (1971) produced immediate falls in the body temperature of rats given 20 mg./kg. of Δ^9 -THC intraperitoneally. In view of an earlier report (Kudrin and Davydova, 1968) that phenitrone (3-[hexahydro-1H-azepin-1-yl]-3'-nitropropiophenone hydrochloride) prevented the development of catalepsy in dogs exposed to hashish smoke, this drug was tested for its ability to reverse Δ^9 -THC-induced hypothermia. When administered intraperitoneally at a dose-level of 10-20 mg./kg. one hour after Δ^9 -THC, it did not reverse the fall in temperature but rather seemed to potentiate the effect. The authors suggested that phenitrone might be displacing Δ^9 -THC from proteins.

The fact that both reserpine and cannabinoids produce hypotension and hypothermia has led Hardman and others (1971) to draw attention to the similarities between the effects of the drugs. However, reserpine acts by depleting brain amines whereas Δ^9 -THC, if it has any effect on these amines, appears to elevate the levels of at least one of them. Any analogy between the modes of action of the drugs is thus somewhat obscure.

Behaviourally, both stimulant and depressant effects have been reported for cannabis extracts and for Δ^9 -THC, especially where spontaneous patterns of behaviour have been studied. In the main, there have been reports of stimulation after low doses of the drug and of depression after high doses (Bose, Saifi, and Bhagwat, 1964; Carlini and Kramer, 1965; Kubena and Barry, 1970). Both Δ^8 - and Δ^9 -THC produce dose-dependent depressions of response in pigeons and rats in operant conditioning situations (Black, Woods, and Domino, 1970; McMillan, Harris, Frankenheim, and Kennedy, 1970; Frankenheim, McMillan, and Harris, 1971). The Δ^9 -compound appeared to be more potent than its isomer; thus, while 2 mg./kg. of the former produced a depression of response in pigeons trained to a multiple fixed-interval schedule of food presentation, 5.6 mg./kg. of Δ^8 -THC was required to produce the same effect.

Avoidance conditioning is also modified by cannabis compounds. For example, Grunfeld and Edery (1969) showed that Δ^9 -THC blocked the conditioned avoidance response of rats in a shuttle-box. Later, Domino, Hardman, and Seevers (1971) demonstrated that

DMHP (10 mg./kg.) reduced avoidance behaviour in a rat pole-jump apparatus of the type first described by Cook and Weidley (1957) and also reduced avoidance behaviour in dogs when given in a dose of 0.25 mg./kg. In 2 out of 3 monkeys, 0.5 mg./kg. (i.v.) of DMHP blocked avoidance responses in a shuttle-box. The drug also appeared to induce a 'confusional state' in monkeys.

In chimpanzees certain aspects of operant behaviour seem resistant to the effects of cannabis. Thus, an oral dose of 1 mg./kg. of Δ^9 -THC or of a marihuana distillate containing the equivalent of this amount of the compound had little effect (Ferraro and Billings, 1972), though there were effects on a schedule involving the reinforcement of low-rate responses. The drug produced a significant decrease in the percentage of correct responses, but in a dose-dependent manner with low doses facilitating the low-rate responses and higher doses suppressing them (Ferraro, Grilly, and Lynch, 1971).

Several groups of workers (Carlini, 1968; Silva, Carlini, Claussen, and Korte, 1968; Dewey, Harris, Howes, and Kennedy, 1969) have reported difficulties in obtaining dose-response relationships with THC's administered repeatedly, especially in behavioural studies. That these difficulties are probably due to the development of tolerance to the effects of the drugs seems to be shown by experiments in which the effect of a daily dose of 1.8 mg./kg. of Δ^9 -THC on operant conditioning in pigeons disappeared within a week (McMillan, Harris, Frankenheim, and Kennedy, 1970; McMillan, Harris, Turk, and Kennedy, 1970). The dose was then increased over the next three weeks to 36 mg./kg., a level at which naive birds were prostrated. In other experiments birds have been brought gradually to a dose of 180 mg./kg., which is lethal to non-tolerant pigeons. Cross-tolerance between Δ^8 - and Δ^9 -THC was also demonstrated. No withdrawal symptoms were noted even when administration of very high doses was sharply discontinued. There is at least one report of a study in which tolerance to Δ^9 -THC was not shown; Lipparini, Scotti de Carolis, and Longo (1969) gave 3 mg./kg. (i.v.) to rabbits daily for 6 days but could find no attenuation of behavioural responses to the drug or its effects on the E.E.G. This seems to be an exceptional case, however, as tolerance to the synthetic cannabinoid DMHP has been demonstrated in both dogs and monkeys (Hardman and others, 1971) and Black and others (1970) using pigeons were able to show that cross-tolerance existed between DMHP and Δ^9 -THC and synhexyl and Δ^8 -THC. These workers found that doses of the drugs could be given as infrequently as once a week yet tolerance still developed, and once established it persisted for long periods. Harris (1971) reported no decrease in tolerance in pigeons 30 days after administration of the last dose.

That tolerance to the behavioural effects of cannabis may not be complete seems to be demonstrated by the work of Bueno and Carlini (1972). Rats injected daily with a marihuana extract became completely tolerant to its blocking action on rope-climbing ability, but these animals were able to respond differentially in a bar-pressing situation to marihuana extract or control solution; that is, the drug was still detected by the animal and had an effect on the central nervous system. Similarly, Harris, Waters, and McLendon (1972) found that monkeys given Δ^9 -THC chronically by the intravenous route rapidly developed tolerance to a drug effect on avoidance responding in a lever-pressing situation, but only partial tolerance on food-reinforced responding. Very little tolerance was noted on gross behaviour, while that which did develop persisted over a 30-day drug-free period. Finally, despite the overwhelming evidence for the development of tolerance to the THC's, there is only one report (Deneau and Kaymakcalan, 1971) of abstinence signs in monkeys following withdrawal of Δ^9 -THC. Variable results in tolerance studies may well reflect the fact that chronic administration of Δ^9 -THC to rats actually increases its metabolism in the liver but not in the lungs (Ho, Estevez, and Englert, 1973). Nevertheless, changes in metabolism or absorption of Δ^9 -THC appear not to be responsible for the development of tolerance to its hypothermic effects, at least in mice (Lawrence and Pertwee, 1973).

The generally depressant effects of cannabis on behaviour are to be expected in view of other aspects of its central nervous system pharmacology. For example, Hardman and others (1971) showed that doses of the synthetic DMHP (1-3 mg./kg.) caused progressive increases in hexobarbital sleeping-time in mice. This is an effect generally associated with depressants of the central nervous system. The hypothermia and analgesia referred to earlier are also manifestations of central depression. It was reported by Hardman and his colleagues (1957) that the depressant action in dogs could be reversed by cocaine, *d*-amphetamine, caffeine, or nalorphine, although the reversal was often only short-lived and succeeded by a prolonged depression. The effects of cannabinoids on cerebral electrical activity are also typical of central nervous system depressants. Domino and others (1971) studied the effects of DMHP in dogs with chronically implanted cortical and subcortical electrodes. Intravenous doses of 0.25 mg./kg. caused the animals to become drowsy within about 20 minutes, with concurrent patterns of high-amplitude low-frequency electrical activity in both areas. Behavioural and electrocortical arousal could be achieved by afferent stimuli of various kinds. Partial antagonism to the drowsiness and the electrocortical effects was produced by 0.25 mg./kg. of

d-amphetamine given intravenously. Essentially similar results were obtained in monkeys (*Macaca mulatta*), and in both species DMHP caused development of high-voltage slow waves more in the frontal portions of the brain than in the posterior portions. This difference was more marked in the monkey than in the dog.

Domino's group argued that since afferent stimuli could still produce arousal in animals showing behavioural and electrocortical depression then DMHP seemed not to affect the threshold to stimulation of the brain-stem reticular formation. They were able to substantiate this argument experimentally by showing that small doses of the drug did not cause significant changes in the threshold to electrical stimulation of the reticular formation. Only when higher doses, which caused coma, were used did higher voltage stimuli need to be applied to produce arousal. Effects of electrical stimulation of the amygdala and the posterior hypothalamus were also studied. In monkeys electrical stimulation of the medial amygdala produced effects reminiscent of olfactory or taste sensations. The administration of DMHP elevated the threshold for these responses. Stimulation of the posterior hypothalamus gave behavioural arousal, which was affected by DMHP in the same way an elevation of the threshold. Antagonism to the effects of the drug on the reticular formation or the hypothalamus, but not on the amygdala, was provided by *d*-amphetamine. Similar effects were observed in the dog, but in both this species and the monkey the effects of DMHP were variable and seemed to be dependent on the level of central nervous system activity of the animals.

Other neuropharmacological studies with DMHP are described in detail by Domino and others (1971). It is sufficient here to record the main conclusions:

1. There is a very close correlation between the electrical activity of the brain and the behavioural effects of cannabinoids.
2. The blockade of conditioned avoidance responses brought about by cannabinoids is due mainly to neither depression of afferent input nor impairment of motor output but rather to confusional or depressional effects on higher brain function.
3. The primary sites of action, at any rate for DMHP, seem to be in the cerebrum, especially in the secondary association cerebral cortices and related subcortical structures.
4. DMHP has little effect on the mesodiencephalic activating system unless large doses are given, when the arousal threshold is elevated.
5. Effects on the amygdala are primarily depressant.
6. Although slight depressant effects on the spinal cord can be detected in high-spinal transected animals, these appear to be

insufficient to account for the body swaying and depression of flexor responses observed after the administration of DMHP to intact animals.

7. Large doses of DMHP produce exaggerated startle responses sometimes including convulsive movements. The mechanism of this is unknown.

Boyd, Boyd, and Brown (1971) also considered that a likely site for the effects of THC underlying the perceptual changes would be the non-primary or association areas of the cerebral cortex. In particular, they studied the frontal lobe postarcuate area of the squirrel monkey which is polysensory in that gross potentials and single-unit responses could be evoked by stimuli of more than one sensory modality. The results, which are described in more detail in Chapter 8 in connexion with the mode of action of cannabis, indicated that Δ^8 - and Δ^9 -THC affected early and late responses in this area in a manner distinct from both ethanol and pentobarbital. It is suggested by these authors that the effects may underlie both the distortions in sensory perception or time-sense noted in humans after marihuana and the hyperreactivity to sensory stimuli observed in animals given the drug.

Martinez, Stadnicki, and Schaeppi (1972), following an earlier report (McIsaac, Fritchie, Idänpään-Heikkilä, Ho, and Englert, 1971) that radio-labelled Δ^9 -THC was selectively distributed in the brains of squirrel monkeys, investigated the effects of Δ^9 -THC upon the E.E.G. of particular brain areas in the rhesus monkey. The drug was infused intravenously into conscious animals in doses of 0.05–12.8 mg./kg. Progressive effects—drowsiness, ptosis, lacrimation, slumped posture, immobility, muscle rigidity, and hyperreactivity to an auditory stimulus—were observed, and there was a dose-related increase in the amount of high-voltage E.E.G. activity in all the brain areas studied (amygdala, cerebellar peduncle, frontal, cortex, hippocampus, nucleus fastigii, occipital cortex, parietal cortex). Rhythmic burst activity (12–16 Hz) also appeared in most areas, but rarely in the hippocampus and never in the frontal cortex. Higher doses of drug (1.6–12.8 mg./kg.) gave high-voltage in-phase epileptiform activity in all areas. A more recent study in rabbits (Willinsky, Scotti de Carolis, and Longo, 1973) demonstrated that 11-hydroxy- and 11-acetoxy- Δ^8 -THC were twice as active as Δ^8 -THC itself in producing E.E.G. changes (disruption of theta waves, appearance of spikes and waves, blockade of the arousal reaction) or behavioural alterations (excitation, exophthalmus, mydriasis, corneal anreflexia, ataxia, and swaying). Cannabinol and cannabidiol were only moderately active at the highest dose used (30 mg./kg., i.v.). The E.E.G. and behavioural changes observed in

rabbits have been equated with the concomitant rapid fall in blood-pressure and slowing of heart-rate; it is suggested that such results may reflect a different mode of hallucinogenesis for THC's from that of other hallucinogens (Fujimori, Trusty, and Himwich, 1973).

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Chapter 6

Drugs affecting Cholinergic Systems

I. ATROPINE-LIKE OR ANTIACETYLCHOLINE DRUGS

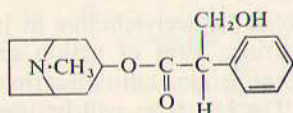
DRUGS which act as competitive antagonists to acetylcholine at its post-synaptic parasympathetic, or muscarinic, sites of action are known variously as atropine-like, anticholinergic, antimuscarinic, cholinolytic, or antiacetylcholine drugs. The last term will be used here.

Alkaloids with antiacetylcholine activity are found in many solanaceous plants, notably *Atropa belladonna* (the deadly nightshade), *Hyoscyamus niger* (the black henbane), and *Datura stramonium* (the Jimson or Jamestown weed, or thornapple). These, and related plants, have been used since very early times as poisons and narcotics and in religious rites and rituals to produce hallucinatory episodes (Schultes, 1969). *Hyoscyamus* was used in ancient Greece as a poison, to produce dementia, and to evoke prophecies. In the Punjab it was known as khoti-bhang and smoked. *Datura* was eaten by Antony's troops during the retreat from the Parthians in 37 and 38 B.C.; many of them developed psychoses before they died (Hoffer and Osmond, 1967). Several uses of *Datura* are described by Schultes (1969) and Brown (1972). Members of South-American Indian tribes, particularly witch doctors, drink an infusion of seeds, leaves, or twigs of the plant. There is an initial violent reaction followed by deep sleep with hallucinations, when the recipient is supposed to acquire divine powers from spirit visitations. In the Jivaro tribes, difficult children are given *Datura* seeds in the hope that the spirits of their forefathers may visit them and admonish their behaviour.

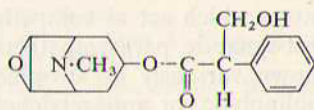
A more macabre use is attributed to the ancient tribes of Bogota, in which the wives and slaves of deceased husbands and masters were given the drug to induce a stuporous state prior to being buried

alive with the departed. The name Jamestown or Jimson weed originates from an episode in the American Civil War when many British troops at Jamestown suffered from *Datura* poisoning, resulting in long-lasting behavioural effects, including hallucinations and amnesia (Hughes and Clark, 1939).

Atropa belladonna also has sinister etymological origins. Extracts of the shrub were used by poisoners in the Middle Ages to cause obscure and lingering deaths, hence Atropa from Atropos the oldest of the three Fates who cuts the thread of life. Belladonna, meaning 'handsome woman', refers to the cosmetic use of the plant extracts to produce mydriasis and hence to give lustre to the eyes. Belladonna poisoning is characterized by various peripheral signs and symptoms including dry mouth, dilated pupils, tachycardia, and urinary retention. In addition there are severe behavioural disturbances with restlessness, excitement, confusion, disturbances of



(6.1)



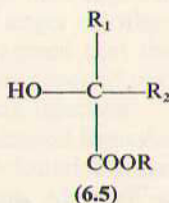
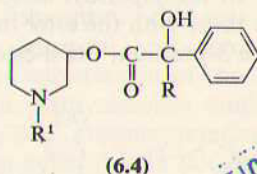
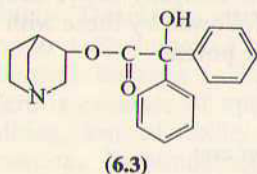
(6.2)

gait and speech, loss of memory, clouding of the senses, and often mania or delirium (Innes and Nickerson, 1970). The young appear to be especially sensitive to the effects of the belladonna alkaloids (Unna, Glaser, Lipton, and Patterson, 1950) and poisoning has often followed the use of atropine or hyoscyne for medicinal purposes in children. The signs of poisoning by anticholinergic drugs in adults has also been long familiar to physicians since the belladonna alkaloids were first used in the middle of the nineteenth century for the treatment of Parkinson's disease. The requirement for massive doses to cope with the centrally-mediated motor deficiencies of the disease has inevitably led to the frequent appearance of toxic psychoses even with the newer synthetic drugs (Pinder, 1972).

Longo (1966) has reviewed the literature appertaining to atropine poisoning; he concluded that the following symptoms had been reported consistently: (a) diminution of the power of concentration and memory; (b) drowsiness, withdrawal, and tendency to sleep; (c) an excitatory effect; (d) loss of coordination of voluntary movements (ataxia) and ability to carry out complex actions (asynergia); (e) hallucinations.

The latter effect seems only to occur after large doses of atropine (6.1) and it may not strictly be correct to describe the drug as an hallucinogenic agent according to the definition outlined in Chapter 1.

The same applies to hyoscine (6.2) which, though widely used as a sedative, produces much the same symptomatology in behaviour as atropine once a certain critical dose is exceeded. Many synthetic antiacetylcholine drugs have been prepared; an account of their chemical development and evolution is given by Inch and Brimblecombe (1974). In the 1950s compounds comparable in activity with atropine, but with more marked central actions, began to emerge. For example, the diphenyl glycollic acid ester of quinuclidinyl-3-ol (6.3), a potent spasmolytic agent, was reported by Randall, Benson, and Stefko (1952) to have pronounced side-effects particularly on the central nervous system. Then in 1958 and 1959, Abood, Ostfeld, and Biel reported studies of the psychotomimetic activity of a series



of piperidyl glycollates of general structure (6.4), which proved to contain some of the most potent compounds having both anti-acetylcholine and hallucinogenic activity.

Structure-activity relationships in the glycollate series have been reviewed by Abood (1968), who compared their activities in both the peripheral and central nervous systems. Peripheral activity was determined by antagonism of acetylcholine-induced effects on the isolated rabbit ileum and in the anaesthetized dog and by the production of mydriasis in the rat. Central activity was measured by increases in motor activity of rats, by increases in the number of errors made by mice while negotiating a swim maze, and by increases in the exploratory activity of mice. The values obtained from these three central parameters were summed and expressed as a behavioural disturbance index (BDI). The compounds discussed by Abood were glycollic esters of *N*-alkylpiperidinols and *N*-alkylpyrrolidinols (6.5). For the glycollic acid moiety his main conclusions were:

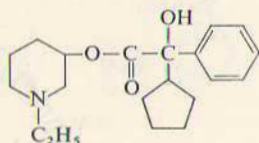
1. The OH group is necessary for maximal activity in both the peripheral and central nervous systems.

2. For activity in the central nervous system, R_1 and R_2 must be the following combinations in decreasing order of potency: cycloalkyl+phenyl; phenyl+phenyl; phenyl+unsaturated alkyl or cycloalkyl+unsaturated alkyl; phenyl+alkyl; cycloalkyl+alkyl; alkyl+alkyl.

For the amino-alcohol moiety, Abood concluded:

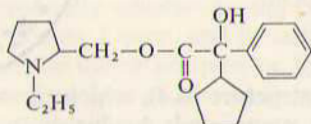
1. In the case of piperidyl or pyrrolidyl esters the N-substituent must be a lower alkyl group (methyl or ethyl) for maximal activity in the central, but not necessarily in the peripheral, nervous system.

2. In the piperidyl series the most potent centrally active drugs were those with the ester in the 4-position, followed by those with it in the 3-position, the 2-esters being the least potent.



30 per cent

+



70 per cent

(6.6)

Whether the BDI is an accurate index of the hallucinogenic potency of these drugs in man remains open to question; insufficient data from human studies are so far available, but where comparisons are possible they suggest that Abood's conclusions regarding relative potencies may also hold for man. Descriptions of the syndrome produced in man by these drugs are, as might be expected, very reminiscent of the accounts of atropine poisoning. The drug which has been most studied is Ditrán (6.6), which is a mixture of two glycolates.

Abood (1968) lists the effects of Ditrán when given by a variety of different investigators in doses of between 1 and 25 mg. by the oral intramuscular, or intravenous routes. Characteristically, in the period 5–15 minutes after intramuscular injection autonomic effects are apparent with mydriasis, dryness of the mouth, tachycardia,

hyper-reflexia, muscle weakness, and dizziness. These effects are accompanied by others described by Abood as emotional-affective symptoms, that is apprehension, feelings of intoxication, giddiness, euphoria, fear, and depersonalization. Afterwards, there follow in turn signs of intellectual impairment and perceptual changes characterized respectively by reduction in the speed and accuracy of problem solving with impairment of concentration and by distortion of images, illusions, and hallucinations. During the period 30-60 minutes after injection a stuporous state may develop with incoherence, somnolence, and disinterest. There have been reports of delirious states occurring in the period 45 minutes-2 hours after injection, characterized by confusion, restlessness, and agitation, motor and mental incoordination, and aimless motor and mental activity. During the same period effects of an apraxic type may also appear with 'impaired motor, amnesic, ideational, and ideomotor abilities'. Between 1 and 2 hours after administration of the drug there is evidence of aphasia and agnosia, with senseless rambling talking, loss of ability to concentrate, and misinterpretation of questions. Emotional signs have also been noted during this period, with sudden outbursts of anger or other emotions, paranoia, panic, and fear. It is generally agreed that these drugs produce amnesia. Abood quotes the time for onset of partial or complete amnesia as being 1-8 hours after drug injection.

This description, paraphrased from Abood's detailed account, will suffice to indicate the profound behavioural changes produced by drugs of the glycollate type. Abood also suggested that there was a close, but not precise, resemblance between the symptoms of schizophrenia and the effects of these drugs. In particular, the panic, the degree of bewilderment and confusion, and the intense sensorial clouding often produced by the glycollates are not normally associated with schizophrenia. There have, however, been several claims that Ditrane and other glycollates produce a schizophrenia-like syndrome (Abood and others, 1959; Meduna and Abood, 1959; Gershon and Olariu, 1960). In view of this, there is interest in a study by Neubauer, Gershon, and Sundland (1966) which was concerned with the effects of Ditrane on a mixed psychiatric population. The patients were divided into five groups on the basis of diagnosis, and all the subjects, 33 in all, were given 0.05 mg./kg. of Ditrane intravenously. The response to the drug was evaluated using a Ditrane rating scale which contained 80 items that had shown changes with Ditrane in previous investigations. The subjects were also asked to copy Bender-Gestalt (B-G) figures. The general effect of Ditrane was to produce a central nervous system depression, with neurological regression and clouding of consciousness being the

most marked effects. The groups diagnosed as being actively schizophrenic showed a relative lack of response to both behavioural and autonomic effects of the drug. This is in general agreement with results obtained by other workers using other psychotomimetic drugs. Neubauer and his colleagues also noted that patients in their chronic inactive group, who all showed diminution of drive, flattening of affect, and personality deficit, tended to be behaviourally and neurophysiologically activated following Ditrán administration.

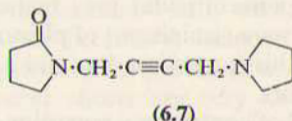
A recent comparative study of the effects in man of atropine, hyoscine, and Ditrán has been made by Ketchum, Sidell, Crowell, Aghajanian, and Hayes (1973). Clinically, the responses to the three drugs were virtually identical, with an induction phase including mainly peripheral and autonomic effects followed by a phase of stupor which was in turn followed by a phase of delirium. The latter phase lasted for 6 to 8 hours in the case of hyoscine and Ditrán, but up to 12 hours with atropine. The mean relative central potencies of the drugs based on three test procedures were atropine (intramuscularly) = 1.0, hyoscine (intramuscularly) = 7.9, hyoscine (intravenously) = 9.5, and Ditrán (intramuscularly) = 1.4. The ED_{50} s of the drugs varied with the test employed but were about 150 $\mu\text{g./kg.}$ for atropine, 100 $\mu\text{g./kg.}$ for Ditrán, and 20 $\mu\text{g./kg.}$ for hyoscine. The effects of the compounds could be reversed by the anticholinesterases physostigmine, sarin, and tetrahydroamino-acridine but not by neostigmine or dyflos. The ineffectiveness of neostigmine is almost certainly due to its inability to penetrate into the central nervous system, but that of dyflos is less easy to explain.

It is clear that the behavioural syndrome produced by anti-acetylcholine drugs differs from that produced, for example, by LSD. This matter was studied by Isbell, Rosenberg, Miner, and Logan (1964), who compared the effects in man of hyoscine, N-ethyl-3-piperidyl benzilate, and LSD. There was development of tolerance to all three drugs on most of the parameters which were measured. There was also a considerable degree of cross-tolerance between the two antiacetylcholine drugs, but this did not extend to all the effects produced. There was little or no evidence of cross-tolerance between LSD and the antiacetylcholine agents, thus adding weight to the view that the two types of compound act by different mechanisms to produce their hallucinogenic effects. The possible modes of action of antiacetylcholine drugs are discussed in Chapter 8. Basically the question to be answered is whether their effects can be explained on the basis of a central antagonism of acetylcholine. Although this cannot be stated with certainty at the present time there is a good deal of evidence to support such a view.

II. ACETYLCHOLINE-LIKE AND ANTICHOLINESTERASE DRUGS

1. ACETYLCHOLINE-LIKE DRUGS

There is very little evidence to suggest that acetylcholine-like drugs have hallucinogenic activity. Most of the compounds with this type of pharmacology are quaternary ammonium salts and thus are incapable of penetrating into the central nervous system. One of the few active tertiary amines is oxotremorine (6.7), which produces a number of effects including tremors, analgesia, and hypothermia as a result of its central actions. In addition, there is one report (George, Haslett, and Jenden, 1962) stating that cats and monkeys which had



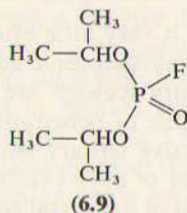
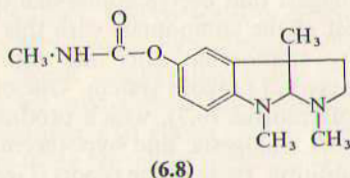
received oxotremorine displayed behaviour which strongly suggested hallucinatory experiences. There has been no confirmatory evidence for this view, and in many experiments in the authors' own laboratories no behavioural effects have been observed in several animal species that are reminiscent of those produced by the classical hallucinogenic drugs.

2. ANTICHOLINESTERASE DRUGS

Administration of drugs which inhibit the enzyme cholinesterase results in the accumulation of acetylcholine at its various neuro-effector sites, including the brain. A good deal of work has been carried out in experimental animals to study the behavioural consequences of this action. Behavioural changes can certainly be detected, but it is by no means clear whether they represent hallucinogenic effects when extrapolated to man.

A clear-cut effect of anticholinesterase agents is to produce a pattern of E.E.G. activity characterized by low-amplitude high-frequency waves (Bradley and Elkes, 1953, 1957). The relationship between this E.E.G. effect and the behaviour of the animal is not clear, however, since, atypically, it is not associated with alert behaviour. On the contrary, anticholinesterase agents commonly cause a depression in behaviour. There is therefore a dissociation between electrocortical activity and behaviour. Cats appear to be somewhat atypical; Feldberg and Sherwood (1954) reported that

after intraventricular injections of the carbamate anticholinesterase agent physostigmine (6.8) and the organophosphate diisopropyl-fluorophosphonate (6.9, dyflos), cats displayed certain motor phenomena and a 'catatonic' stupor. These effects, they claimed, resulted



from inhibition of cholinesterase with accumulation of acetylcholine in the region of the periventricular grey matter. The authors suggested that the effects were reminiscent of phenomena seen in schizophrenic patients, but this suggestion does not seem to have received any subsequent support.

There is a good deal of controversy regarding possible behavioural effects of anticholinesterase agents in man. This controversy is mainly concerned with possible psychological or psychiatric sequelae of chronic exposure to such agents. Discussion of this matter is inappropriate to the present book, which is concerned specifically with acute effects of drugs. That some anticholinesterase agents can have fairly acute effects seems to be demonstrated by the work of Grob, Harvey, Langworthy, and Lilienthal (1947). They gave 1-2 mg. of physostigmine daily by intramuscular injection to 60 normal subjects. Symptoms apparently originating in the central nervous system included, in order of frequency, excessive dreaming, insomnia, jitteriness, restlessness, increased tension, emotional lability, subjective tremulousness, nightmares, headache, increased libido, giddiness, drowsiness, paraesthesia, mental confusion, visual hallucinations, tremor, and pains in the legs of sciatic distribution.

More recently, Bowers, Goodman, and Sim (1964) have reported the effects on male volunteers of an organophosphate, code number EA-1701, the chemical nature of which was not revealed in the paper. Neither the dose of agent nor its precise site of application was specified, though it is stated that it 'was applied by a micrometer syringe to various body sites', where it was presumably absorbed percutaneously. Initially, subjects reported vague feelings of fatigue and difficulties in concentration. Later 'jitteriness' or 'tenseness inside' was reported; during this period many subjects experienced difficulty in maintaining a train of thought and became depressed, irritable, and listless. There were minor difficulties with orientation,

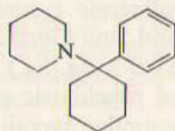
mainly slow responses to date, time, and location. However, all the subjects retained insight, were aware of the decrements in their performance, and there were no illogical or inappropriate trends in thought or speech.

It is clear from these two studies that anticholinesterase agents can produce acute changes in behaviour, but the changes are diverse and varied and it is doubtful whether they can be classified as hallucinatory in nature. Certainly on the basis of the criteria used in this book to define hallucinogens, anticholinesterase drugs do not produce hallucinogenic effects in man.

III. PHENCYCLIDINE

1-(1-Phenylcyclohexyl)piperidine (**6.10**, phencyclidine, Sernyl) is included in this chapter because it bears a certain structural resemblance to some antiacetylcholine drugs and because the descriptions of its behavioural effects are very similar to those of the classical antiacetylcholine hallucinogens.

Phencyclidine was introduced as a powerful analgesic capable of producing sufficient sensory blockade at the subcortical level to



(**6.10**)

enable minor surgical procedures to be carried out (Johnstone, Evans, and Baigel, 1959; Collins, Gorospe, and Rovenstine, 1960). It soon became apparent that the drug produced marked behavioural side-effects (Chen, 1958; Catenacci, 1958). Patients showed pronounced agitation, anxiety, illusions, delusions, and hallucinations, with interference with thought processes. In many cases a state of catatonic stupor developed. The hallucinations were usually unpleasant, as indeed is the whole experience resulting from phencyclidine (Ban, Lohrenz, and Lehman, 1961). Nevertheless, the drug has been used as an illicit hallucinogen under the name of 'Hog' (Lindgren, Hammar, Hessling, and Holmstedt, 1969).

Cohen, Rosenbaum, Luby, and Gottlieb (1962) claimed that the effects of phencyclidine were similar to those seen in chronic schizophrenics, but two other groups (Chen, Ensor, Russell, and Buhner, 1959; Meyer, Greifenstein, and Devault, 1959) thought that they

were the result of sensory deprivation. The incidence of hallucinogenic effects may approach 50 per cent in adult patients, but there is a lower incidence in the elderly (Lister, 1966). Muir, Evans, and Mulcahy (1961) reported that the drug gave adequate analgesia in 78 per cent of infants being treated for burns, but there was a 50 per cent incidence of hallucinations and crying in the children. Meyer and his colleagues (1959) and Levy, Cameron, and Aitkins (1960) have emphasized the unpredictability of responses to the drug, with route of administration being an important factor. The dosage of phencyclidine to produce central side-effects is between 0.05 and 0.2 mg./kg. (Brown, 1972); the effects are apparent minutes after an intravenous injection, but they are less marked, though more prolonged, following intramuscular administration. Orally, the drug is much less effective.

A study of the metabolic fate of phencyclidine was carried out by Ober, Gwynn, Chang, McCarthy, and Gazko (1963), using radio-labelled drug given to monkeys in doses ranging from 2 to 6 mg./kg. About 60 per cent of the radioactivity appeared in the urine within 12 hours, nearly all in the form of metabolites. The main metabolite was a conjugated non-phenolic dihydroxyphencyclidine. Only about 1-2 per cent of the doses were recovered from the faeces.

Some justification for including phencyclidine in a discussion of hallucinogens affecting cholinergic systems is to be found in the study by Neubauer, Sundland, and Gershon (1966). They compared the effects of phencyclidine (0.1 mg./kg.) and Ditrane (0.05 mg./kg.) given by mouth to a mixed psychiatric population. The two compounds showed a markedly similar overall profile of action although there were differences of detail. Thus, phencyclidine had a more marked effect on perceptual changes while Ditrane produced more neurological impairment, anxiety, and hallucinations. Succinic acid, contrary to a previous report by Gershon and Olariu (1960), failed to show any antagonism to the effects of phencyclidine.

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Chapter 7

Miscellaneous Hallucinogens

IN addition to the relatively well-defined classes of chemical compounds described in the preceding chapters, there exists a number of unrelated substances which possess hallucinogenic properties. It is not the purpose of this monograph to discuss all the drugs reported to produce such effects in man, and reference will be made only to those which fall into our present definitions and whose action is well documented. However, compendiums of these compounds have been compiled and particular reference should be made to the monograph of Usdin and Efron (1967).

I. MUSCIMOL

1. AMANITA MUSCARIA

Certain extracts of the fly agaric mushroom, *Amanita muscaria*, are probably the oldest known hallucinogenic drugs, although their use for intoxicating purposes is now virtually restricted to the tribes of northern Siberia. Wasson (1970) has propounded a compelling thesis that the legendary *Soma*, described and deified in Sanskrit texts of the second millenium B.C., was in fact *Amanita muscaria*, and the ancient Chinese drug of immortality, *Chih*, may have been the same. Wasson's extensive research and self-administration of the drug allows certain conclusions to be drawn regarding the hallucinogenic properties. Thus, (a) the effects appear within 15–20 minutes and last for several hours; (b) the soporific action induces a 2-hour sleep from which the subject cannot be roused but in which he is still aware of sounds—hallucinations and coloured visions appear in this half-sleep, which are apparently susceptible to self-manipulation; (c) upon waking, a feeling of elation often lasts for 3–4 hours and the subject is capable of both performing and enjoying feats of extraordinary physical effort; (d) the active principles pass into the urine, and it is the practice of the Siberian tribes to collect and re-use this several times before it is finally discarded.

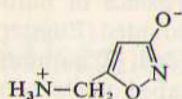
Amanita muscaria is widespread throughout the world except for the tropic zones. It is the most notorious member of the poisonous *Amanita* genus although several other members are considerably more toxic. Toxicity is related to the presence of peptidic toxins, but it is interesting that *Amanita citrina*, the yellow mushroom, contains bufotenin and other hallucinogenic indoles (Wieland, 1968). There is no evidence, however, that this mushroom has ever been used for intoxicating purposes, while early reports of the presence of bufotenin in *Amanita muscaria* have now been largely discounted (Eugster, 1969). The fly agaric grows from July until the end of autumn, preferably under fir or beech trees, as an egg-shaped white cap. The cap bursts open the outer shell and the surface becomes brilliant red with the residue which remains as white spots regularly distributed over it. The mushroom may reach 25 cm. in height and an average specimen weighs 60–70 g. The name 'fly agaric' is derived from the insect-killing properties of the mushroom, although its action is poor in comparison to modern insecticides and is more in the nature of a temporary stupefaction.

Amanita muscaria is normally ingested in the natural state (Brekman and Sam, 1967; Wasson, 1970). It is gathered in the spring or summer, less often in the late autumn, and swallowed whole in a slightly desiccated state. Other methods use infusions, after soaking for five to six days in water, which are sometimes taken with *Epilobium angustifolium*, the French willow; the latter mixture is boiled to produce a thick, sweet liquor to which, in modern times, underproof vodka is often added.

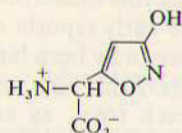
2. THE ACTIVE PRINCIPLES OF *Amanita muscaria*

The discovery by Schmiedeberg and Koppe in 1869 of the parasympathetic stimulant muscarine served to conceal for almost a century the true nature of the centrally active principles of *Amanita muscaria* (Eugster, 1960; Wilkinson, 1961). Muscarine is present in only very low concentrations, less than 0.0002 per cent of the fresh mushroom, and its relatively weak activity on oral administration clearly ruled out its candidacy as the hallucinogenic principle. Moreover, mushrooms of the genus *Inocybe* contain much larger amounts of muscarine, up to 0.037 per cent in some cases, but produce toxic states distinctly different from the hallucinoses experienced by users of *Amanita muscaria*. Other substances which act upon central cholinergic systems, such as atropine and hyoscyamine, have also been detected, but in amounts that exclude them as possible causes of the hallucinogenic effects. The mushroom also contains very small quantities of unidentified indole derivatives, but it is clear

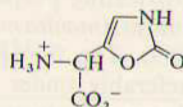
that the centrally active components are the isoxazole derivatives, muscimol (7.1, pantherine) and ibotenic acid (7.2), and the oxazolone, muscazone (7.3). Ibotenic acid, which is the zwitterion of α -amino- α -(3-hydroxy-5-isoxazolyl)acetic acid, is present to the extent of 0.03–0.1 per cent of fresh *Amanita muscaria* and can be regarded as the precursor of muscimol, by decarboxylation, and



(7.1)



(7.2)



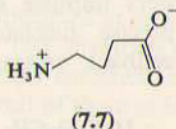
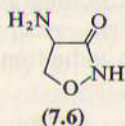
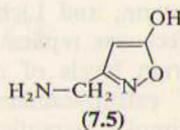
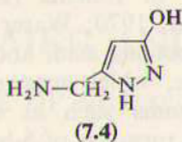
(7.3)

muscazone, by photochemical rearrangement. Muscimol may be the hallucinogenic principle of the fly agaric and pharmacological investigations of the mushroom have, in recent years, focused on this very polar and extremely water-soluble enol-betaine.

In animals, muscimol is about 5–10 times more potent than either of the amino-acids in producing hyperthermia, catalepsy, sedation, and myoclonic cramps (Waser, 1967; Theobald, Büch, Kunz, Krupp, Stenger, and Heimann, 1968; Scotti de Carolis, 1969). Indeed the original bioassay for the centrally active principles of *Amanita muscaria* were based upon the narcosis-potentiating effects of the extracts. Experiments in man have confirmed these results and duplicate the ethnopharmacological reports of Wasson. Waser (1967) describes the effects of self-administration of 10–15 mg. of muscimol as '... intense hallucinations as with LSD were missing ... there resulted considerable disturbances of psychic functions, such as orientation in space and time, visual perception, process of thinking, speech, and some new psychic phenomena of illusions and echo pictures'. Higher doses tended to produce severe intoxication in man, with painful muscular twitching, considerable agitation, and vivid hallucinations. Similar doses of ibotenic acid or muscazone were virtually without hallucinogenic activity but showed only some unpleasant effects on the peripheral circulation. Muscimol can be detected in the urine of human subjects, again providing confirmation of Wasson's studies in Siberia. Clearly, a study of the animal and human metabolism of the compound would give interesting results, but no experiments of this type have yet been reported. Indeed, in view of the hydrophilic nature of the very polar muscimol structure the question needs to be answered as to whether muscimol reaches the brain. Is the active hallucinogen a muscimol-like metabolite which subsequently passes into the urine, where it can be detected?

3. THE MODE OF ACTION OF MUSCIMOL

Few details of structure-activity relationships in the muscimol series are available, but it is significant that neither the aza analogue (7.4) nor the isomeric compound (7.5) show the potent central depressant and hallucinatory effects of muscimol itself (Loev, Wilson, and Goodman, 1970). However, the closely related antibiotic oxamycin (7.6) produces mental confusion, acute psychotic episodes, convulsions, and other abnormal behavioural states in



man reminiscent of the isoxazoles contained in *Amanita muscaria* (Farnsworth, 1968). The structural analogy between muscimol and the inhibitory synaptic transmitter γ -aminobutyric acid (GABA, 7.7) has prompted several studies of the effects of the isoxazole on the firing of central neurons when administered by microiontophoresis. Both muscimol and GABA are powerful inhibitors of spinal interneurons and Renshaw cells in cats while ibotenic acid is a more powerful excitant than L-glutamic acid (Johnston, Curtis, De Groat, and Duggan, 1968). This is in accord with the general observation that α -decarboxylation of an excitant amino-acid leads to an amine or amino-acid with depressant properties, and may well explain the intense taste-enhancing effects of ibotenic acid in man (Wieland, 1968). Thus, if monosodium glutamate produces a depolarization of taste receptors then it is likely that the more potent ibotenic acid will have an even greater effect on those receptors. The pharmacological relationship is confirmed in the snail, *Helix aspersa*, where neurons in the suboesophageal ganglion are inhibited and the cell membrane potential hyperpolarized by ibotenic acid and glutamate while other neurons are excited by GABA and muscimol with depolarization of the cell membrane (Walker, Woodruff, and Kerkut, 1971).

Muscimol is only a weak, non-competitive inhibitor of the specific GABA uptake process in rat cerebral cortex, and it is probably not

transported efficiently by this system and not at all by uptake systems for other putative transmitters such as aspartate, glutamate, 5-hydroxytryptamine, and noradrenaline (Johnston, 1971; Logan and Snyder, 1971). It has therefore been suggested that inefficient removal of muscimol from the environment of GABA receptors may be an important factor contributing to its central effects. Certainly, muscimol had no effect on dopamine, 5-hydroxytryptamine, or acetylcholine receptors in *Helix aspersa*, although it resembles other more familiar hallucinogenic substances such as LSD in increasing brain levels of 5-hydroxytryptamine in rodents (König-Bersin, Waser, Langemann, and Lichtensteiger, 1970; Waser and Bersin, 1970). This effect was replicated by ibotenic acid, and both drugs reduced forebrain levels of dopamine, which may explain their production of extrapyramidal symptoms such as catalepsy in animals. Muscimol apparently reduces turnover of 5-hydroxytryptamine and lowers impulse flow in serotonergic neurons, but whether the precise mechanism involves receptor stimulation and negative feedback or trans-synaptic induction has still to be determined.



It is not possible at present to decide whether muscimol produces its hallucinogenic effects by stimulation of inhibitory GABA receptors or by a serotonergic mechanism, or even whether both or neither is involved. X-ray crystallography of muscimol has demonstrated a conformation in which the side-chain is directed towards the ring oxygen but is not coplanar with the isoxazole ring, the torsion angle being 60° (Brehm, Hjeds, and Krogsgaard-Larsen, 1972). This agrees well with the reported conformation of GABA (Steward, Player, Quilliam, Brown, and Pringle, 1971) but poorly with the energetically favoured extended conformations calculated by molecular orbital analysis (Kier and George, 1970, 1973). Nevertheless, it is likely from recent studies of GABA analogues of restricted conformation (Beart, Johnston, and Uhr, 1972; Beart, Uhr, and Johnston, 1972) that both the interaction of GABA with postsynaptic receptors and the GABA transport system involve GABA in an extended, and not a folded, conformation. It is pertinent at this point to recall the possible hallucinogenic actions of amino-oxyacetic acid (7.8), an agent which increases endogenous brain levels of GABA by competitively inhibiting GABA- α -ketoglutarate transaminase, the enzyme which controls the rate-limiting step in GABA metabolism (Van Gelder, 1966). This compound produces retropulsion in mice (Henry, 1971), a property which has previously been correlated with hallucinogenic effects in the case of LSD

(Woolley, 1955). If effects on brain GABA systems are causally related to the hallucinogenic properties of muscimol then amino-oxyacetic acid seems worthy of investigation in more precise tests for central action. A recent neuropharmacological study in cats (Gottesfeld, Kelly, and Renaud, 1972) suggests that the delayed inactivation of synaptically released GABA, produced by amino-oxyacetic acid, need not be the result of inhibition of GABA transaminases but be due to other, as yet unidentified, mechanisms.

II. NUTMEG AND MACE

1. THE USE OF NUTMEG AND MACE

Nutmeg and mace both come from the nutmeg tree, *Myristica fragrans*, native to the Indonesian archipelago and now cultivated also in the Caribbean. There are over 100 members of the genus *Myristica* but only *M. fragrans* contains sufficient of the essential oils to be worthy of cultivation. The fruit of the tree is rather similar to an apricot, and when ripe it splits to reveal a shiny brown seed-coat. The shell is covered in a bright crimson network or arillus, which after drying becomes mace, while the seed within the shell is the nutmeg.

The history of use of the two spices is very old. Though unknown to the ancient Greeks and Romans they were used by Indian and Arab civilizations as early as 700 B.C., being later introduced into Europe by Arab merchants and subsequently by Portuguese and Dutch traders (Weil, 1967; Kalbhen, 1971; Forrest and Heacock, 1972). Like other cooking spices such as pepper, paprika, caraway, fennel, cloves, and aniseed, nutmeg has always been important in folk medicine, and it has been used at various times as an analgesic, stomachic, digestive, hypnotic, aphrodisiac, and amenorrhœal agent. A reputation as an abortifacient led to a brief but spectacular resurgence of its fading popularity in medicine, and medical journals at the turn of the last century contained numerous reports of nutmeg poisoning (Weil, 1965). Nevertheless, it is only in the last two decades that nutmeg has been deliberately used solely for its intoxicating properties, almost exclusively in the United States. The legal availability of this cheap spice has doubtless led to its widespread use by young people and convicts as an alternative to marihuana and LSD. The use of nutmeg in the kitchens of American penal institutions has apparently been stopped as a result of this abuse (Weil, 1967; Kalbhen, 1971), which has been thoroughly documented in a study by Weiss (1960) at the New Jersey State Prison in Trenton.

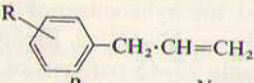
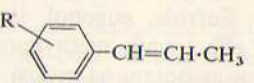
Reports of nutmeg intoxication date back to the Middle Ages when physicians first began to report on the effects of overdoses of the spice administered for medicinal purposes. Thus, the English physician William Cullen wrote of a patient in his *Treatise on the Materia Medica* in 1789: '... about one hour after he had taken it (nutmeg), he was seized with a drowsiness, which gradually increased to a complete stupor and insensibility ... waking from time to time he was quite delirious; and he thus continued alternately sleeping and delirious for several hours'. The personal experience of the Breslau physiologist J. E. Purkinje (1829) suggested a similarity to hashish intoxication: '... my movements ... were lost in dream pictures. ... I went forward in a dream. ... Time seemed long ... dreams and physical activity battled with one another'. Similar experiences were subsequently reported with mace (Watson, 1848) and a recent summary (McCord and Jervey, 1962) of intoxications with the spices attributes them to a central nervous system depressive effect with periods of stimulation and associated respiratory and cardiovascular difficulties. Experiences with nutmeg vary widely, but Payne (1963) has provided perhaps the best description of its effects when he administered 14 g. of whole nutmeg to two students. About five hours later each experienced a leaden feeling in the extremities and a nonchalant detached mental state described as 'dreamlike'. Both complained of dry mouth and thirst and experienced rapid heart-rates and palpitations. Nausea, vomiting, and abdominal cramps, a common feature with nutmeg, were absent but the subjects became hyperactive and agitated. Extreme drowsiness occurred about 7 hours after the symptoms began and continued for the next 24 hours; recovery was complete but both reported a sense of unreality for up to 60 hours after the oral dose of nutmeg. More recent descriptions of single intoxications are available (Fras and Friedman, 1969; Painter, Shanor, and Winek, 1971). Nutmeg is normally taken orally, stirred into hot liquids, about 5-30 g. being the usual dose. Snuffing is a relatively rare form of administration which might conceivably give more rapid intoxication as a result of better uptake into the circulation. Nutmeg intoxication is characterized by a subsequent prolonged aversion to the spice.

2. THE ACTIVE PRINCIPLES OF NUTMEG

A detailed chemical analysis of nutmeg was reported as early as 1907 (Power and Salway, 1907, 1908) and established the presence of 25-40 per cent of fatty oils (nutmeg butter), 8-15 per cent of volatile oils, and 45-60 per cent of structural materials like cellulose. Therapeutic uses of nutmeg have usually involved the volatile oils, although

Warburg (1897) expressed doubt as to their contribution to the intoxicating effects of the spice. Nevertheless, it was soon clear that the residue from which the volatile oils had been removed had no effect on animals (Cushny, 1908) and that the pronounced central effects in cats were best produced by the higher-boiling fractions of oil of nutmeg (Wallace, 1903; Jurss, 1904; Dale, 1909). Gas-chromatographic analysis of the volatile oils has established that they consist of a terpene fraction, which constitutes over 80 per cent of the total distillate and includes such major components as α -pinene and sabinene, and a higher-boiling aromatic fraction (Shulgin, Sargent, and Naranjo, 1967). The terpene fraction may merely serve to assist absorption of the psychoactive aromatics through the gut, since turpentine has a similar composition but lacks any reputation as an intoxicant. The aromatic fraction constitutes 10–15 per cent of the volatile oils and contains a number of propenylbenzenes, chiefly myristicin, elemicin, and safrole (Table 7.1). Mace has a somewhat similar composition.

Table 7.1.—COMPOSITION OF THE AROMATIC FRACTION OF OIL OF NUTMEG (data from Shulgin and others, 1967).

	Name	Amount (mg.) in 20 g. Nutmeg*		Name	Amount (mg.) in 20 g. Nutmeg
3,4-OCH ₂ O	Safrole	39			
3-OCH ₃ -4-OH	Eugenol	5	3-OCH ₃ -4-OH	Isoeugenol	6
3,4-(OCH ₃) ₂	Methyl-eugenol	18	3,4-(OCH ₃) ₂	Methylisoeugenol	11
3,4,5-(OCH ₃) ₃	Elemicin	70	3,4,5-(OCH ₃) ₃	Isoelemicin	3
3,5-(OCH ₃) ₂ -4-OH	Methoxy-eugenol	8			
3-OCH ₃ -4,5-OCH ₂ O	Myristicin	210			

*20 g. of whole nutmeg is approximately the oral dose required to produce hallucinogenic symptoms in man.

Safrole is a major component (over 80 per cent) of oil of sassafras which has not been reported as a psychoactive beverage despite its widespread use in sassafras tea and as an internal medicament. The various eugenols also comprise a major part of another familiar natural product, oil of cloves, which is similarly innocuous. Elemicin codistils with myristicin and it has been suggested that the variable amounts of the former in natural oil of nutmeg and in naturally-derived myristicin account for the variable degree of reported psychoactive effects in man (Shulgin and others, 1967). Certainly,

naturally-derived myristicin containing elemicin, given in doses of 400 mg. (equivalent to about 40 g. of whole nutmeg), failed to reproduce exactly the typical nutmeg intoxication in man, although the observed symptoms were suggestive of psychotropic effects in 6 out of 10 subjects (Truitt, Callaway, Braude, and Krantz, 1961). Myristicin is a weak inhibitor of monoamine oxidase both *in vitro* and *in vivo*, but there is some disagreement as to whether it and its congeners shorten (Truitt, 1967) or potentiate (Seto and Keup, 1969) barbiturate sleeping times in rodents. Both viewpoints may be correct, however, because administration of a variety of propenylbenzenes to rats and guinea-pigs produces an initial hyperactivity followed after 30 minutes by sedation, immobility, and lack of response to stimuli (Oswald, Fishbein, Corbett, and Walker, 1971a,b). This biphasic response of stimulation followed by tranquillization is also characteristic of the effects of nutmeg and mace in man and other higher species and is not produced by administration of nutmeg from which myristicin has been removed (Truitt, 1967). In a recent study in rats and mice (Cesario de Mello and Carlini, 1973), myristicin and elemicin, as well as total oil of nutmeg or oil of mace, caused catatonia, decreased motor activity, and impaired rope-climbing and bar-pressing performance in a dose-dependent manner. Safrole, eugenol, isoeugenol, and methylisoeugenol were without effect while methyleugenol was only weakly active. Elemicin was twice as potent as myristicin but had only 33–65 per cent of the activity of Δ^9 -THC in the same test situations. Peak effects were reached after 15–30 minutes and disappeared within 60–90 minutes.

Myristicin resembles other compounds which contain the methylenedioxyphenyl moiety in acting as a synergist to the action of many insecticides as a result of its inhibition of microsomal enzymes responsible for detoxification of insecticides. It is therefore possible that myristicin acts mainly as a synergist to other hallucinogenic factors in oil of nutmeg, and the superior hallucinogenic properties of whole nutmeg or total oil of nutmeg may be due to the necessity for such synergism between the individual propenylbenzenes (Seto and Keup, 1969). Clearly, studies are required of the effects of systemic administration of single compounds derived from nutmeg and of mixtures of known composition in order to eliminate spurious results arising from different rates of absorption and metabolism following oral administration.

3. THE METABOLISM OF PROPENYLBENZENES

The major metabolic pathway (61–76 per cent) in mice for safrole, myristicin, and their congeners, after oral administration, is cleavage

of the methylenedioxy moiety and expiration of the methylene carbon as carbon dioxide (Kamienski and Casida, 1970). Nevertheless, the propenyl side-chain is a highly reactive grouping, and Shulgin (1966) has suggested that such compounds might alternatively be metabolized by established routes to the corresponding amphetamines (Fig. 7.1), a group of substances known to be potent hallucinogens (see Chapter 3). Barfknecht (quoted by Shulgin and others, 1967) claims to have detected amphetamine in the urine of rats treated with oral allylbenzene, while ninhydrin-positive materials which might be amphetamines have been found after chromatographic separation of the urine metabolites in rats given oral

Table 7.2.—METABOLIC CONVERSION OF PROPENYLBENZENES INTO NITROGEN-CONTAINING COMPOUNDS IN RODENTS (data from Oswald and others, 1969, 1971a, b)

Propenylbenzene*	Species	Type of ω -Aminopropiophenone†		
		Dimethyl-amino	Pyrrolidino	Piperidino
Myristicin	Rat	—	+	+++
	Guinea-pig	—	+++	+
Safrole	Rat	++	+	+++
	Guinea-pig	+++	—	—

*Asarone, elemicin, eugenol, isosafrole, and other propenylbenzenes also undergo similar biotransformations to the three types of ω -aminopropiophenone, although the proportion of each metabolite has yet to be determined. (Oswald, Fishbein, Corbett, and Walker, 1972a, b).

†+++ = major metabolite, ++ = minor metabolite, + = trace metabolite.

myristicin, safrole, and other nutmeg constituents (Oswald, Fishbein, and Corbett, 1969). Further study of these materials by mass spectrometry, and their identity with authentic samples prepared by unequivocal synthesis, has shown them to be not amphetamines but ω -aminopropiophenones (Oswald and others, 1971a, b; McKinney, Oswald, Fishbein, and Walker, 1972). It is interesting that O-demethylation and side-chain oxidation to the corresponding benzoic or phenylpropionic acids are reported as the major metabolic routes in the rat for 4-methoxyallylbenzene and 4-methoxypropenylbenzene, respectively contained in tarragon oil and anise or fennel oils (Solheim and Scheline, 1973). There is still no evidence, therefore, to demonstrate that amphetamines are the metabolically-derived psychoactive principles of nutmeg and mace, and the only unequivocal identification of metabolites with such properties are the ω -aminopropiophenones (Fig. 7.1, Table 7.2). Nevertheless,

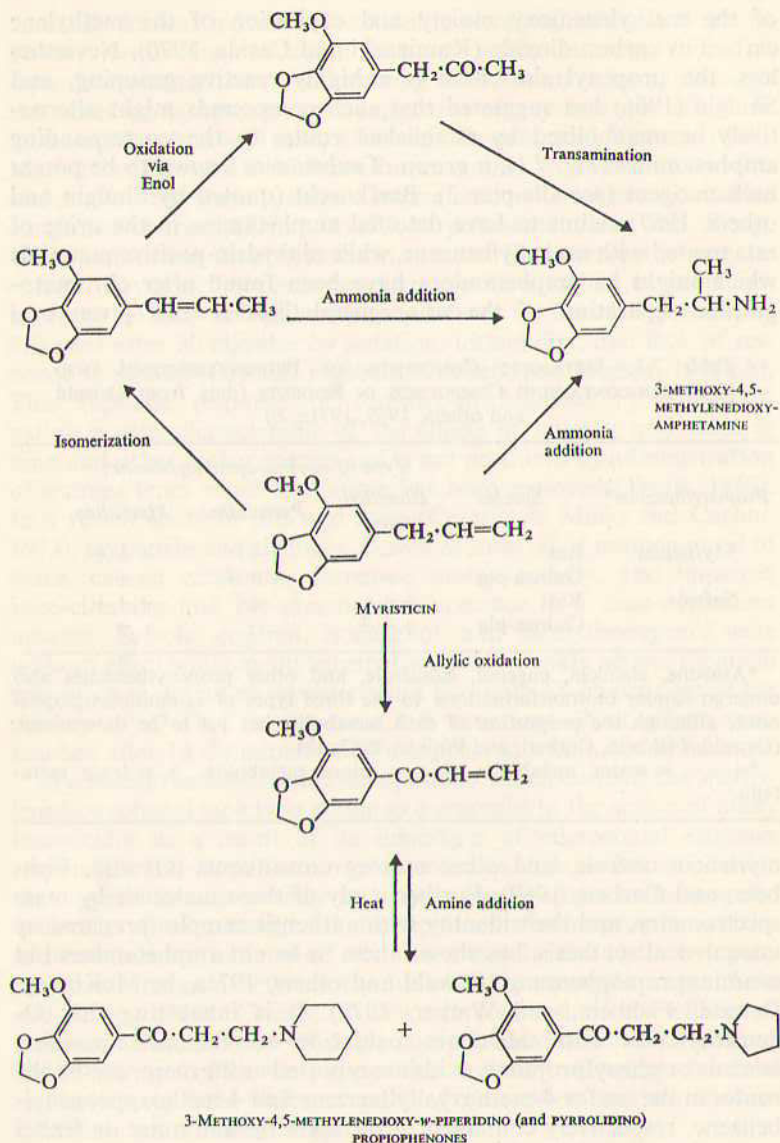
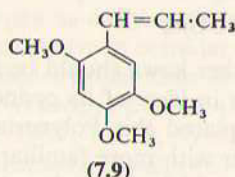


Fig. 7.1.—Proposed metabolic transformations of propenylbenzenes into psychoactive amphetamines and ω -aminopropiophenones, using myristicin as an example. There is little evidence for the former, but the latter is a well-established route in rodents.

Braun and Kalbhen (1972) claim to have detected the formation of 3-methoxy-4,5-methylenedioxyamphetamine from myristicin, though examination of their chromatograms suggests that it is more probably the corresponding ω -aminopropiophenone. More recently, the same workers (Braun and Kalbhen, 1973) have unequivocally identified this amphetamine by mass spectrometry of their chromatographically-separated metabolites, produced by incubation of myristicin *in vitro* with rat liver.

There seems little justification in trying (Kalbhen, 1971) to correlate the known hallucinogenic potencies of amphetamines with the content of the corresponding propenylbenzenes, from which they are supposedly derived, in particular samples of nutmeg and mace. Certainly, myristicin failed to produce the E.E.G. activation and associated behavioural changes in rats, cats, and rabbits that characterized the action of several psychotomimetic amphetamines including its analogue 3-methoxy-4,5-methylenedioxyamphetamine (Florio, Fuentes, Ziegler, and Longo, 1972). It is significant, however, that ω -aminopropiophenones are susceptible to further biotransformation, particularly reduction to the corresponding ephedrine (Vree, Muskens, and Van Rossum, 1972), which are known to produce euphoriant effects in man (*see* Chapter 3). Furthermore, propiophenones related to the metabolites of propenylbenzenes



have depressant effects in the central nervous system (Moffett, Hanze, and Seay, 1964), and the latter are also structurally related to the neuroleptic butyrophenones like haloperidol. Indeed, several ω -piperidinopropiophenones prepared during the investigation of structure-activity relationships in the haloperidol series showed a biphasic pharmacological profile very like that of the nutmeg metabolites (Usdin and Efron, 1967; Zirkle and Kaiser, 1970).

It is pertinent that 1-(2,4,5-trimethoxyphenyl)prop-1-ene (asarone, 7.9), an isomer of elemicin, is even more potent than myristicin, elemicin, or safrole in potentiating barbiturate sleeping times in rodents (Seto and Keup, 1969) and probably undergoes similar biotransformations to ω -aminopropiophenones (Oswald and others, 1969). There is no evidence, however, that either oil of calamus,

which contains asarone as its main constituent, or extracts of *Asarum europoeum*, from which asarone is obtained commercially, have ever enjoyed use as intoxicants. The root of *Acorus calamus*, another source of asarone, has been used as a mild stimulant by North-American Indians and in Europe as a substitute for tobacco during the depression of the 1930s (Hoffer and Osmond, 1967). Asarone seems to have the facility to antagonize the action of many hallucinogens in rats, its action against mescaline being more effective than chlorpromazine (Dandiya and Menon, 1965). Nevertheless, Hoffer and Osmond (1967) report the production of LSD-like symptoms in experienced drug-users following the mastication and ingestion of 2–10 in. of acorus root: ‘... seemed to be walking one foot above the ground. The effect was very unlike amphetamine...’. More precise experiments are clearly needed to confirm these observations, and it will be interesting to see whether the ω -amino-propiofenones listed in Table 7.2 produce effects in man that can account for the psychotomimetic properties of nutmeg and related substances or whether some other metabolite or as yet unidentified constituent is responsible.

III. KAWA (KAVA-KAVA)

1. PIPER METHYSTICUM

It is a moot point whether kawa should be included in a discussion of hallucinogenic drugs in view of its pronounced soporific effects. Indeed, Lewin (1931) placed this Polynesian beverage in his hypnotica category together with more familiar drugs of this type such as the barbiturates, paraldehyde, and potassium bromide. Kawa does resemble the classical hallucinogens, however, in consistently altering thought, mood, and perception, without causing serious disability, while there is some degree of chemical similarity between the structures of the active constituents of kawa and the tetrahydrocannabinols of hashish. The beverage normally induces a form of euphoria, described as a happy state of complete comfort and peace, with ease of conversation and increased perceptivity, followed by muscular fatigue and restful sleep. The experience is pleasant and is generally free from hangover or other after- and side-effects. Lewin provides a typical description of kawa experience: ‘The eye sees objects before it but is unable to identify them with exactness ... the ears hear everything but the individual is unable to account for what he hears. Everything becomes more and more diffuse ... consciousness remains unaffected’. Stronger versions of kawa or

greater doses rapidly produce sleep, often preceded by a state of nervous trembling and total loss of muscular control.

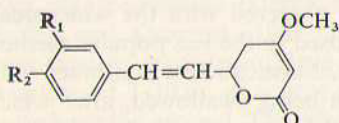
Kawa is prepared from the roots of *Piper methysticum*, a piperaceous shrub which grows throughout Oceania and much of Australasia. The preparation forms part of the ceremonial and ritual associated with the important role which kawa plays in the religious, cultural, and social life of the natives of this part of the world (Ford, 1967). Fresh roots give a more potent form of kawa than do dried roots, a feature also observed with the widespread procedure of pre-mastication as opposed to the less popular method of crushing the roots between stones. Mastication is continued until the root is fine and fibrous, no juice being swallowed, after which the pulp and juices are mixed by hand for several minutes with fresh cold water before being filtered through a sieve of coconut fibre. The resulting liquid resembles an infusion of coffee with milk and contains a fine detritus of the root. The taste varies according to the method of preparation and thereby according to the amount of resin extracted by the preparative procedure, and it can range from insipid to very bitter, aromatic to biting, soapy to astringent.

2. THE ACTIVE PRINCIPLES OF KAWA

Chemical investigation of the pharmacologically active constituents of *Piper methysticum* began as early as the mid-nineteenth century, but it is perhaps more instructive to consider what has been found by modern analytical techniques rather than discourse at length on the various chemical isolations used in the past (Klohs, Keller, Williams, Toekes, and Cronheim, 1959; Klohs, 1967). Gas chromatography coupled with mass spectrometry has allowed identification of sixteen acids from kawa root (Achenbach and Karl, 1971), including caproic and 4-oxononanoic acids as well as a number of benzoic, cinnamic, and hydrocinnamic acids. The volatile members of this group are probably responsible more for the characteristic odour of kawa than for its pharmacological effects, although it is likely that some of them, particularly 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxy-cinnamic acids, act as biosynthetic precursors for the active constituents. The latter are undoubtedly a series of α -pyrones, the first of which was identified in 1861, and a full list has now been compiled by the use of modern chromatographic procedures (Young, Hylin, Plucknett, Kawano, and Nakayama, 1966; Jössgang and Molho, 1967; Csupor, 1970a, b; Achenbach, Karl, and Smith, 1971). These are kawain (7.10) and methysticin (7.11) and their dihydro derivatives (7.12 and 7.13), dihydrokawainol (7.14), yangonin (7.15), 11-methoxyyangonin (7.16), desmethoxyyangonin

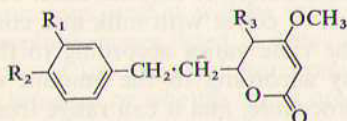
(7.17), 5,6,7,8-tetrahydroangonin (7.18), 11-methoxynoryangonin (7.19), and 5,6-dehydromethysticin (7.20): other minor constituents will doubtless be discovered in different samples of kawa from various locales.

The effects of individual α -pyrones are reputed to be not as prominent as those of the whole mixture imbibed as kawa (Klohs and others, 1959), and it is clear that many of these compounds act



(7.10) $R_1 = R_2 = H$

(7.11) $R_1R_2 = O \cdot CH_2 \cdot O$

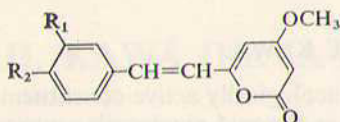


(7.12) $R_1 = R_2 = R_3 = H$

(7.13) $R_1R_2 = O \cdot CH_2 \cdot O$; $R_3 = H$

(7.14) $R_1 = R_2 = H$; $R_3 = OH$

(7.18) $R_1 = R_3 = H$; $R_2 = OCH_3$



(7.15) $R_1 = H$, $R_2 = OCH_3$

(7.16) $R_1 = R_2 = OCH_3$

(7.17) $R_1 = R_2 = H$

(7.19) $R_1 = OCH_3$; $R_2 = OH$

(7.20) $R_1R_2 = O \cdot CH_2 \cdot O$

synergistically with one another (Meyer, 1967). Experiments in man suggest that the α -pyrones of kawa act chiefly as central muscle relaxants of the mephesisin type, but their activity in this respect is considerably less than that of modern synthetic drugs (Pfeiffer, Murphree, and Goldstein, 1967). Indeed, doses of 800–1200 mg. daily are required to control epileptic seizures, for example, and these high doses reproduce the characteristic allergic reactions, particularly yellowing of the skin, seen in chronic kawa drinkers. The euphoria induced by kawa is probably due to the ease with which the lactones enter the central nervous system because, like their close structural relatives the tetrahydrocannabinols, they are but poorly soluble in water while retaining good lipid solubility.

Pharmacological evaluation and structure-activity relationships of kawa lactones are due chiefly to Meyer and his group in Freiburg (Meyer, 1967; Kretzschmar and Meyer, 1969; Kretzschmar, Meyer, Teschendorf, and Zöllner, 1969; Meyer and Kretzschmar, 1969). All of the pyrones present in kawa, as well as a number of synthetic analogues, are effective as anticonvulsants, antispasmodics, and local anaesthetics, differences in action being of degree rather than of kind.

The reported activity of aqueous extracts of kawa (Buckley, Furgiuele, and O'Hara, 1967), in which the α -pyrones are very poorly soluble, is probably due to the small amounts of these compounds which are in fact extracted (Kretzschmar and others, 1969). Intravenous administration provides little difference in the potencies of the pyrones, which decrease in the sequence kawain > methysticin > yangonin, but intraperitoneal injection provides more variation in results because of different rates of absorption and transport. Thus, methysticin is by far the most potent α -pyrone in this latter mode of administration, doses of 200–300 mg./kg. raising the LD₅₀ of strychnine by 5–6-fold, a dose at which mephenesin is relatively ineffective. All three types of pharmacological activity depend essentially upon the 4-methoxy- α -pyrone moiety, particularly the fully reduced type, while potency is enhanced by an unsaturated hydrocarbon bridge between this and the benzene ring and by methylenedioxy substitution in the latter. Kawa remains a curiosity among the natural hallucinogens, possessing definite effects on the central nervous system but lacking the vivid and dramatic actions associated with the magical drugs of South and Central America.

IV. TARAXEIN

Perhaps no other single substance has aroused more controversy in the field of brain research than taraxein, the only hallucinogen isolated from human sources (Heath, 1959; Hoffer and Osmond, 1967). Such was the opposition to Heath's isolation of a unique serological fraction from schizophrenic patients that his work tends now to be overlooked and there are few reports on taraxein since the mid-1960s. Taraxein remains an enigma, but Heath's critics are often unaware that his findings have been independently corroborated by many laboratories (*see* Hoffer and Osmond, 1967; Walaas, 1967). The numerous failures to isolate taraxein may be due to the extreme sensitivity of the method and the material itself to factors such as pH and temperature.

Heath first reported on taraxein in 1956 at the 112th Meeting of the American Psychiatric Association. He subsequently used the protein-like substance to induce reversible symptoms of schizophrenia in non-schizophrenic volunteers and to produce catatonia and focal changes in electroencephalograms from the septal regions of rhesus monkeys similar to those observed in schizophrenic patients. Taraxein appeared to be a classical hallucinogen, producing consistent changes in mood, thought, and perception, in well-conducted, double-blind experiments. Thus, the normal volunteers suffered

catatonic stupor or excitement, thought process changes such as blocking, autism, deprivation, and persecution delusions, together with depersonalization and auditory, but not visual, hallucinations (Heath, Leach, Byers, Martens, and Feigley, 1958; Heath, Martens, Leach, Cohen, and Feigley, 1958). Taraxein was claimed to produce more typical schizophrenic reactions than true hallucinogens like LSD, mescaline, and psilocybin in man (Silva, Heath, Rafferty, Johnson, and Robinson, 1960) and in monkeys (Melandar and Martens, 1958), while responders to one of these drugs were reported to respond markedly to the others. Studies in many animal species have confirmed the toxic effects of schizophrenic plasma, to an extent that justified devotion of a major part of the 1965 NATO Advanced Study Institute to serum factors in schizophrenia (Walaas, 1967).

Taraxein is probably a protein, being heat-labile, non-dialysable, and precipitated by ammonium sulphate (Heath, 1961). Heath has consistently believed that taraxein increased the permeability of the blood-brain barrier, thereby allowing toxic substances normally present in the blood but unable to get into the brain to produce a toxic effect. Certainly, schizophrenic serum enhanced penetration of various dyes into the brain (Heath, 1959) and markedly increased the toxicity of adrenolutin to animals (Melandar and Martens, 1958). The toxic substance may actually be part of taraxein because it has been shown that a small active molecule can be dialysed away from the proteinaceous part of the serum factor, suggesting a possible exchange of this small molecule *in vivo* between proteins located on either side of the blood-brain barrier (Hoagland, 1960; Hoagland, Pennell, Bergen, Saravis, Freeman, and Koella, 1962). The small molecule may be a biogenic amine or some derivative thereof since catecholamines and monoamine oxidase inhibitors potentiated the toxic effects of taraxein in animals (Hoagland, 1964; Walaas, 1967).

The case for or against taraxein remains unproven. Early in 1967 Heath and his colleagues published a series of papers outlining their concept of schizophrenia as an auto-immune disease (Heath and Krupp, 1967; Heath, Krupp, Byers, and Liljekvist, 1967). They claimed to have isolated antibodies from the septal and basal caudate regions of schizophrenic brains which were not present in non-schizophrenic brains. Serum globulins from all types of schizophrenics induced physiological and behavioural abnormalities in monkeys; the active principle was similar to immunoglobulin G and was capable of combining with neural cell nuclei in the septal region and basal caudate nucleus. This area of the brain might therefore contain a unique antigen against which antibody can be created and which is capable of combining with neural cell nuclei

to induce aberrations. Heath suggests that taraxein is the antibody and that its toxic action involves impairment of neurohormonal conduction. There is no evidence, however, that injection of either chronic (Rogeness and Weil-Malherbe, 1968) or acute (Ancill, Harston, Neubauer, and Redfern, 1970) schizophrenic serum produces any alterations in brain amine metabolism in animals. Nevertheless, it is pertinent to note that conjugates of various hallucinogenic agents, including mescaline and 2,5-dimethoxy-4-methylamphetamine, with polyglutamic acid and rabbit serum albumin were capable of eliciting the production of specific antibodies upon injection into rabbits (Van Vunakis, Bradvica, Benda, and Levine, 1969). Perhaps immune processes are involved in the production of tolerance and cross-tolerance, so common to the chronic and repeated use of many hallucinogenic drugs.

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Chapter 8

Mechanisms of Action of Hallucinogenic Agents

It is unlikely that all types of hallucinogenic agents share a common mode of action. At the present state of knowledge it seems reasonable to group the agents into three main categories: the sympathomimetic amines (indolealkylamines and phenylalkylamines); the anticholinergic drugs; the cannabinoids. The assumption will be made that drugs within these classes act by similar, if not identical, mechanisms. Whether this assumption will stand the test of time remains to be seen. There will be no discussion of miscellaneous agents which cannot be fitted into any of the three categories. They represent such a heterogeneous collection that no commonality of action can be discerned, and, in any case, relatively little information is available about them.

I. SYMPATHOMIMETIC AMINES

All the drugs in this group are capable of producing effects equivalent to stimulation of the sympathetic nervous system. This immediately raises the possibility that this property is in some way related to the hallucinogenic actions of the drugs. There appears, however, to be no simple relationship between sympathomimetic and hallucinogenic activities. This may to some extent be due to the fact that not all sympathomimetic agents are equally capable of penetration into the central nervous system. Nevertheless, other factors are clearly important since amphetamine, for example, a centrally-acting sympathomimetic amine, produces general central excitation but not, in the acute phase, hallucinogenic effects. Despite this there have been suggestions (Rothlin, Cerletti, Konzett, Schalch, and Taeschler, 1956; Zehnder and Cerletti, 1956) that a stimulation of central sympathetic centres by LSD is a main factor in its hallucinogenic action. Such an effect could be produced in a variety of ways;

the action on the postulated centres could be direct or indirect or could result from inhibition of reciprocal inhibitory systems. In any event it would seem probable that at the biochemical level the drug action could result from some kind of interaction with central chemical transmitter substances or their receptors. To this end a great deal of work has been carried out with LSD and other drugs in the sympathomimetic group to define their interactions with various putative central transmitters.

1. EFFECTS ON BRAIN LEVELS OF 5-HYDROXY-TRYPTAMINE

For some time this work was concentrated on 5-hydroxytryptamine (4.3, serotonin, 5-HT), owing mainly to the findings by Gaddum (1953, 1954) and Woolley and Shaw (1954) that LSD in low concentrations antagonized the actions of 5-HT on various peripheral tissues. This led to the suggestion that a similar central antagonism of 5-HT might be responsible for the hallucinogenic actions of LSD. This theory received a setback when it was found that drugs even more potent than LSD as peripheral antagonists of 5-HT were virtually devoid of hallucinogenic activity. The best known example is 2-bromoLSD (BOL-148), which appears to have no hallucinogenic activity except at high doses (Cerletti and Rothlin, 1955) but the same general statement applies to other derivatives of LSD (Isbell, Miner, and Logan, 1959). The possibility has always existed that measures of peripheral anti-5-HT activity are of little relevance to the situation in the central nervous system, and a recent finding by Boakes, Bradley, Briggs, and Dray (1970) seems to bear this out. They found that LSD when applied by microiontophoresis to single neurons in the brain-stem of the decerebrate cat, or administered intravenously, antagonized 5-HT excitation of these neurons. On the other hand, BOL-148 rarely exhibited such antagonism.

Another possibility is that LSD produces its effects by interaction with 5-HT receptors and again evidence obtained from peripheral tissues would support such a view. Thus, LSD mimics the excitatory effects of 5-HT on the rat uterus (Costa, 1956) and clam heart (Welsh, 1957) and on the formation of 3',5'-adenosine phosphate by tissue particles from the liver fluke (Mansour, Sutherland, Rall, and Buedling, 1960). It has been claimed (Wright, Moorhead, and Welsh, 1962; Beernink, Nelson, and Mansour, 1963) that there is a correlation between the hallucinogenic potencies of a series of drugs related to LSD and their 5-HT-like potencies. It seems that higher doses of LSD have these actions while lower doses act as 5-HT antagonists.

It is clear that sufficient evidence exists to justify further studies into the possible interaction between hallucinogenic sympathomimetic amines and 5-HT. It is now equally clear that possible interactions with other putative transmitter substances will require investigation since there is an increasing awareness of the presence of reciprocal systems in the central nervous system. These systems are normally in a state of equilibrium, upsets in which can be brought about by drugs or disease to result in profound behavioural changes in the organism as a whole. Both biochemical and pharmacological techniques have been used to study the possible role of hallucinogenic drugs in bringing about such changes.

Freedman and his colleagues were responsible for much of the early work on the effects of LSD on the metabolism of brain amines. In 1961 Freedman reported that LSD (130–1500 $\mu\text{g./kg.}$) administered to rats caused small (c. 20 per cent) but reproducible increases in levels of brain 5-HT. There were concomitant falls in levels of brain noradrenaline, an effect which was attributed to the excitation produced by the drug. Szára (1962) and Freedman (1963) showed that psychoactive congeners of LSD had similar effects but that the weakly hallucinogenic BOL-148 did not. The increase in 5-HT levels was confined to the high-speed particulate fraction of brain homogenates (Freedman and Giarman, 1962), suggesting a specific action in a particular cellular compartment. Similar increases in brain 5-HT levels after LSD administration were found in the cat, dog, guinea-pig, and rabbit (Freedman and Aghajanian, 1966). The precursor of 5-HT is the amino-acid 5-hydroxytryptophan (5-HTP) and its metabolic product is 5-hydroxyindole-3-acetic acid (5-HIAA) (Fig. 8.1). Freedman and Giarman (1962) were unable to detect any influence of LSD on either 5-HTP decarboxylase or monoamine oxidase, the enzymes responsible respectively for the biosynthesis and degradation of 5-HT. Neither could they detect any action on the brain transport system for 5-HTP, and so they concluded that LSD enhanced the binding of 5-HT by brain granules. An important feature of this work was that the peak of the effect on brain 5-HT corresponded well with the onset of behavioural, electrocortical, and autonomic effects (Freedman and Giarman, 1962; Freedman, Appel, Hartman, and Molliver, 1964). Similar effects on brain amine levels were also obtained with other hallucinogenic derivatives of lysergic acid and with mescaline and psilocybin (Freedman, 1963).

To investigate in more detail the role of brain amines in the action of LSD and related agents, Freedman and his colleagues tested the effects of LSD on animals which had been pretreated with other agents known to interact in some way with brain amines. For

example, rats were pretreated with the 5-HT antagonist BOL-148 (1800 $\mu\text{g./kg.}$, 10 minutes before 520 $\mu\text{g./kg.}$ of LSD) and it was found that the rise in brain 5-HT levels was reduced. The aminergic blocking drug chlorpromazine (2 mg./kg., 1 hour prior to 1300 $\mu\text{g.}$ of LSD) similarly reduced the LSD effect on 5-HT levels by up to 64 per cent. Reserpine is a drug which releases 5-HT and inhibits its binding capacity; after reserpine treatment, LSD was still capable of causing elevations of brain 5-HT levels. Both LSD and reserpine appeared to affect binding in the particulate rather than the supernatant fraction, adding weight to the view that LSD in some way

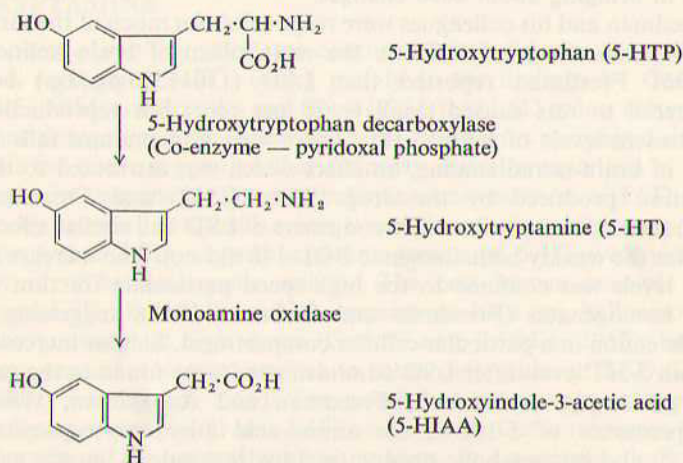


Fig. 8.1.—Biosynthesis and degradation of 5-hydroxytryptamine.

enhances or induces 5-HT binding by brain granules. It should be realized that this describes the locus but not the function of 5-HT, and therefore it does not explain the behavioural consequences of the interaction between LSD and 5-HT. It is clear, however, that the behavioural effects of LSD are modified in animals in which mechanisms for the regulation of brain amines have also been modified. Thus, rats given a single dose of reserpine and tested 3–4 days later, when brain 5-HT and other amines are still depleted, show a prolonged behavioural response to a subthreshold dose of LSD (40 $\mu\text{g./kg.}$). Freedman (1963) also reported that the human response to LSD was exacerbated by pretreatment with reserpine. Fourteen schizophrenic women were given 120 $\mu\text{g.}$ of LSD two days after 10 mg. of reserpine. The effects lasted longer and all the patients felt that the effects of LSD were less pleasant than when it was taken in a control period.

The question arose as to whether these changes in brain amines represented a specific response to the hallucinogenic drugs or whether they could also be achieved by other less specific methods, notably stress. Freedman, Barchas, and Schoenbrun (1962) reported briefly that certain procedures calculated to produce exhaustion produced similar effects to LSD on levels of 5-HT and noradrenaline in the brain. The results were given in more detail by Freedman (1963), and are summarized in *Table 8.1*. It is difficult to assess the implications of these findings, since it would be necessary to know whether

Table 8.1.—EFFECTS OF STRESSFUL PROCEDURES ON BRAIN AMINE LEVELS IN RATS (after Freedman, 1963)

<i>Form of Stress</i>	<i>Percentage Change in 5-HT</i>	<i>Level of Significance</i>	<i>Percentage Change in Noradrenaline</i>	<i>Level of Significance</i>
Swim in warm water	+20	<0.001	-26	<0.001
Swim in cold water	+16	<0.001	-14	<0.05
Hypophysectomy and cold swim	+17	<0.01	-10	<0.10
18-24 hours in cold room	+9	<0.10	-20	<0.01
24 hours on treadmill	+10	<0.05	-10	>0.10

the mechanisms whereby the drug-induced changes are brought about are identical or not. Perhaps the most likely explanation is that the effects produced by hallucinogenic drugs are stressful in nature and hence may induce the same changes as non-specific stresses.

Nevertheless, since the original work of Freedman's group the consensus of opinion among the numerous studies of the effects of hallucinogenic drugs on brain amines is that the observed changes are specific responses to the drugs and are of some consequence in their mode of action. It is clear, however, that hallucinations do not necessarily accompany elevated brain 5-HT levels, and their occurrence may depend upon other factors. Thus, such drugs as monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines, and butyrophenones, all cause elevations of levels of the amine in the brain without causing hallucinations (Brawley and Duffield, 1972). Conversely, it has been reported (Ferguson, Henriksen, Cohen, Mitchell, Barchas, and Dement, 1970) that the substance *p*-chlorophenylalanine, which specifically depletes brain 5-HT has behavioural effects in cats which may be hallucinogenic. If the hallucinogenic agents have a specific effect it seems to be in decreasing the rate of turnover of 5-HT, a view strengthened by the finding

that reductions in the rate of urinary excretion of the 5-HT metabolite 5-HIAA follows LSD administration to animals. Rather more direct evidence for a reduced turnover rate of brain 5-HT following LSD was obtained by Lin, Ngai, and Costa (1969). They developed a method of estimating the turnover rate in the brain of unanaesthetized rats during infusion of small doses of ^{14}C -labelled tryptophan, and showed that LSD infused at a rate of 0.6 mg./kg./hour for 40 minutes did reduce the rate of turnover, that is the brain 5-HT concentration increased when LSD was infused with tryptophan. BOL-148 infused in doses 5-fold greater than those of LSD had no such effect. From their findings the authors suggested that LSD interacted with brain 5-HT receptors and in so doing it might facilitate the effects of the amine on brain neurons.

In 1966 Freedman and Aghajanian drew together all the knowledge available at that time, and speculated about the sequence of events which followed LSD administration. It is of interest to repeat their speculation here and to examine recent evidence to see whether it strengthens or weakens their case. It was suggested that when a dose of LSD is given sufficient to produce observable behavioural and autonomic effects, it first acts at receptor sites closely related to 5-HT. The LSD then leaves the brain; while this occurs noradrenaline is released or used and there is a binding of 5-HT in a component of the 'particulate' fraction. This 'secondary' binding may represent a shift at a critical site and may be in response to effects initiated by the drug. Certainly, the increase in 5-HT levels begins when the drug starts to be cleared whereas acute effects on behaviour and on autonomic functions are seen prior to the rise in 5-HT levels. The point is made that there are various processes in dynamic equilibrium and measurements made at given points in time give values which are the net result of a number of active processes. More recent work by Freedman's group (Ziegler, Lovell, and Freedman, 1973) supports the idea that LSD alters tissue-binding capacity for 5-HT, and suggests that it decreases 5-HT turnover through an inhibition of neuronal firing. The decreased turnover may also be mediated by a mechanism which protects 5-HT from deamination by monoamine oxidase as well as one which involves 5-HT uptake or storage.

2. LOCUS OF ACTION

The first stage in the proposed process is an interaction between LSD and a receptor, presumably that for 5-HT. There is now a good deal of evidence to support the view that LSD does have a post-synaptic action. Much of the work has been carried out with neurons in the raphe nuclei of the medulla, pons, and mid-brain. These

neurons are known to contain 5-HT (Fuxe, 1965) and it was shown by Aghajanian, Foote, and Sheard (1968) that LSD, in systemics does of 25–50 $\mu\text{g./kg.}$, inhibited the rate of firing of the majority of neurons in the dorsal and median raphe nuclei of the rat. Later work established that mescaline, DOM, and *N,N*-dimethyltryptamine shared this inhibitory effect of LSD, while atropine, hyoscine, and chlorpromazine did not (Foote, Sheard, and Aghajanian, 1969; Aghajanian, Foote, and Sheard, 1970). BOL-148 and methysergide were only weakly active in comparison with LSD (Aghajanian, Sheard, and Foote, 1970). Monoamine oxidase inhibitors injected systemically also depress firing rates of raphe neurons, but this effect, unlike that of the hallucinogenic agents, is abolished by pretreatment with the 5-HT-depleting agent *p*-chlorophenylalanine and is therefore unlikely to be a post-synaptic phenomenon (Aghajanian, Graham, and Sheard, 1970). The most likely explanation is that suggested by Brawley and Duffield (1972), that the increased amounts of 5-HT present in the synaptic cleft after monoamine oxidase inhibition would induce tachyphylaxis, a common feature of the central action of 5-HT (Roberts and Straughan, 1967; Johnson, Roberts, and Straughan, 1969). In contrast, the action of LSD on these raphe neurons does appear to be post-synaptic, for Couch (1970) demonstrated that they were excited by iontophoretically applied 5-HT and that LSD applied by the same method blocked the excitation caused either by 5-HT or by electrical stimulation of the midbrain reticular formation. Aghajanian, Haigler, and Bloom (1972) also showed that iontophoretically applied LSD or 5-HT inhibited the spontaneous firing of 5-HT-containing neurons in the midbrain raphe nuclei.

All this evidence taken together lends considerable support to the view that LSD and related hallucinogens act as competitive antagonists for 5-HT at receptors, at least as far as raphe neurons are concerned, where 5-HT seems to act as an excitatory transmitter substance. Inhibition of these neurons would be expected to decrease the rate of 5-HT turnover and hence to lead to elevated levels of the amine in the brain. Whether this effect is specific to the raphe nuclei and what its consequences are in terms of changes in behaviour remain unanswered questions, although the finding of Boakes and his colleagues (1970) referred to above seems to indicate that LSD can act as a competitive antagonist to 5-HT on neurons in other regions of the brain.

Another area of the brain where both 5-HT- and noradrenaline-containing nuclei have been demonstrated by histochemical techniques is the lateral geniculate nucleus in the visual pathway (Fuxe, 1965). Clearly, both amines are likely to be neurotransmitters in this

nucleus and there have been a number of studies of the actions of substances applied to the neurons by microiontophoresis. The studies resulted in two apparently contradictory conclusions. Curtis and Davis (1962), using pentobarbitone-anaesthetized cats, found that 5-HT, other tryptamine derivatives, lysergic acid derivatives, and some catecholamines, depressed firing rates of lateral geniculate neurons evoked by impulses arriving along the optic nerve. The drugs had no influence on firing induced by antidromic stimulation or by iontophoretically applied L-glutamate. It was proposed that 5-HT did not have a post-synaptic action on these neurons, that is it was not the natural transmitter, but that it, together with the other indolealkylamines and catecholamines, either blocked the release of an excitatory transmitter from the optic nerve terminals or prevented its access to post-synaptic receptors. Phillis, Tebėcis, and York (1967) used cats anaesthetized either with halothane or with methoxyflurane-nitrous oxide and showed that 5-HT, noradrenaline, and dopamine depressed the responses of geniculate neurons to optic nerve and light stimulation but also to antidromic stimulation and to chemical stimulation by glutamate or acetylcholine. These workers concluded that 5-HT and catecholamines had post-synaptic depressant effects on lateral geniculate neurons. It was probably of significance that Curtis and Davis ejected the drugs from their micro-pipettes with currents of 10–40 nA whereas Phillis and his colleagues used currents of up to 100 nA. In an attempt to resolve the apparent discrepancies, Tebėcis and Di Maria (1972) carried out similar experiments in which they used both high and low concentrations of 5-HT. Their results suggested that 5-HT had two types of depressant actions on the neurons. Low doses apparently blocked the excitatory action or the release of the transmitter from optic nerve terminals on to lateral geniculate neurons, while higher doses had a direct depressant action on the post-synaptic membrane. The latter effect may indicate an inhibitory transmitter role for 5-HT as suggested by Phillis and others (1967). In the context of this book the most interesting finding by Tebėcis and Di Maria was that 4-hydroxytryptamine and LSD also had these two types of depressant action on lateral geniculate neurons, and presumably mediated by 5-HT receptors. The catecholamines dopamine and noradrenaline appeared to have only post-synaptic depressant actions.

Evidence of a rather different kind for the stimulation of 5-HT receptors by LSD was obtained by Andén, Corrodi, Fuxe, and Hökfelt (1968), and subsequently extended to psilocybin, and to N,N-dimethyltryptamine and its 5-methoxy derivative (Andén, Corrodi, and Fuxe, 1971; Fuxe, Holmstedt, and Jonsson, 1972). The model used in these studies to evaluate changes in central

5-HT receptor activity was the extensor hindlimb reflex of the acutely spinalized rat which had been shown previously to be highly dependent upon 5-HT receptor activity (Andén, Jukes, and Lundberg, 1964). All the drugs mentioned above caused hyperextensions and athetoid movements in this preparation, that is effects similar to those seen after administration of the 5-HT precursor, 5-HTP. Tryptamine was only weakly effective and bufotenin was without effect. The active drugs also reduced the degree of depletion of 5-HT in the brain brought about by α -(3,4-dihydroxyphenyl)propylacetamide, an inhibitor of tryptophan hydroxylase; that is, the drugs reduced the 5-HT turnover. It was concluded by the authors that this decrease in turnover might be due to a receptor feedback mechanism initiated by stimulation of 5-HT receptors by the drugs. The same stimulation might also produce the increase in turnover of brain noradrenaline which was also observed.

3. THE 5-HT RECEPTOR

Models

The evidence for the existence of 5-HT or tryptaminergic receptors in the brain is strong and it seems likely that LSD and related drugs are capable of interacting with these receptors. The amphetamine derivative, DOM, also appears to act on these or similar receptors (Wallach, Friedman, and Gershon, 1972). There have been suggestions by Smythies and his colleagues as to the nature of the 5-HT receptor. In 1969, Smythies, Benington, and Morin claimed that construction of molecular models suggested that the 5-HT binding site could be composed of the two ring oxygens (O1 and O2) of DNA deoxyribose on either side of the intercalation site (one hydrated and one not). It was suggested that the lipophilic indole ring of 5-HT could stack with the intercalated base pairs and bond by its hydroxyl hydrogen to O1 (via H_2O) and directly by its nitrogen to the deoxyribose oxygen. The indolic nitrogen, the third bonding group of 5-HT, could bond to a third atom (O3) located in protein in apposition to DNA. This positioning of a molecule of 5-HT would tend to stabilize the helix and so inhibit RNA polymerase. This model was used by Smythies and his colleagues to include Δ^9 -THC in their theory, a somewhat surprising inclusion in view of the very different spectrum of effects of the cannabinoids compared to tryptamines and phenylalkylamines. Nevertheless, Smythies claimed that a variety of hallucinogenic drugs could bind to the proposed site and hence block the action of 5-HT. Thus, methoxylated amphetamines could bond in various ways to O1 and O2, while N,N-dialkyltryptamines could bond to O3 but would fail to bond

effectively to 01 and/or 02. Both LSD and Δ^9 -THC could block the site by virtue of their close steric fit. Smythies has subsequently expanded and amended this model. His picture is now of four polypeptide chains which form part of the receptor protein and are capable of accommodating 5-HT or other neurotransmitters at various places (Fig. 8.2).

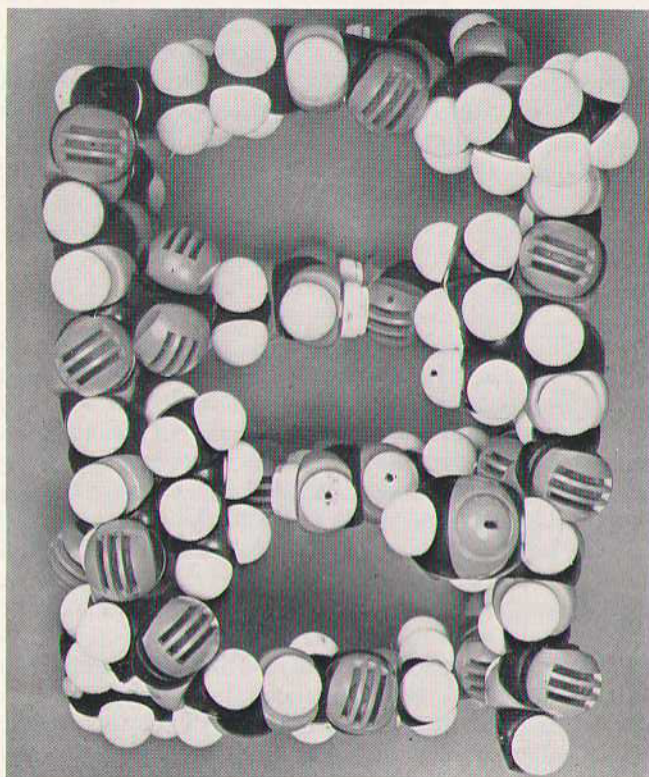


Fig. 8.2.—CPK molecular model of the four polypeptide chains forming possible receptor sites for several neurotransmitters. The essential sequences of the two primary chains (underneath are (a) right: -Glu-x-Arg-x-Glu-x-Glu-; (b) left: -Arg-x-Arg-x-Glu-x-Arg-. Those of the two secondary chains (on top) are (a) right: -Gly-x-Gly-Pro-x-Ileu-x-His-x; (b) left: -x-Asp-x-Ileu-Pro-Gly-x-Gly.

An interesting development from the Smythies concept of the 5-HT receptor was published by Carnegie, Caspary, Smythies, and Field (1972). They noted that lymphocytes from patients with multiple sclerosis and other degenerative neurological diseases were

sensitized to the encephalitogenic basic protein from human myelin (EF) (Caspary and Field, 1970). Patients with malignant neoplasia also possess lymphocytes which are able to respond to EF and to a synthetic peptide, Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg. The latter corresponds to that region in the human protein which induces experimental autoimmune encephalomyelitis in guinea-pigs, the so-called 'encephalitogenic determinant' (Field, Caspary, and Carnegie, 1971). In 1971, Carnegie drew attention to the close structural resemblance between this determinant and the proposed 5-HT receptor of Smythies, Benington, and Morin. However, the model proposed by Field and his colleagues did not agree entirely with the structural requirements for encephalitogenicity stated by Westall, Robinson, Caccam, Jackson, and Eylar (1971); in particular, the latter authors did not assign a key role to glutamic acid. In an attempt to resolve the conflict Smythies (1971) and Smythies, Benington, and Morin (1972) proposed a further model in which the peptide was placed in an anti-parallel- β -pleated sheet conformation.

Field and his co-workers (1971) had shown that 5-HT blocked the reaction between sensitized human lymphocytes and EF or the synthetic peptide, providing it is added before the antigen. Other substances, acetylcholine, succinylcholine, histamine, adrenaline, noradrenaline, and dopamine were without effect, and 5-HT had no effect in systems where the antigen was structurally unrelated to EF. In view of these findings, Carnegie and co-workers (1972) studied the effects of various indole derivatives related to 5-HT and of other hallucinogenic agents on the interaction of human encephalitogenic protein with lymphocytes from patients with degenerative neurological diseases. The results are summarized in *Table 8.2*. They are of interest in that drugs known to be hallucinogenic partially block the reaction between protein and lymphocytes. There is not, however, a good correlation between hallucinogenic potency and potency in producing blockade, nor is the blocking action limited to hallucinogens. The results are therefore probably best considered as interesting observations with potential importance in elucidating the mode of action of hallucinogens vis-a-vis 5-HT, but it would be premature to draw any firm conclusions from them at this stage.

The Smythies concept of the 5-HT receptor was used further to predict the activities of some compounds. As their test for hallucinogenic activity they used rats producing Bovet-Gatti profiles on the Sidman avoidance schedule. This behavioural procedure had been claimed previously to discriminate between hallucinogenic and other centrally-acting drugs (Smythies, Bradley, and Johnston, 1967, 1968). They found that 4-methoxyamphetamine (3.4) was 'a very potent disrupting drug in rats and produces a typical hallucinogenic

profile at 3 mg./kg. (equivalent to mescaline at 25 mg./kg.)'. Its N,N-dimethyl derivative was inactive at 25 mg./kg. DOM (3.28) was active in rats at 2.5 mg./kg. whereas its N,N-dimethyl derivative was quite without effect at 20 mg./kg. These results suggest that if the compounds bond to the receptor they do so via their amino moiety, and the prediction was made that 3-methoxyamphetamine, which had not been tested, would be an active hallucinogen. However, structure-activity relationships in the amphetamine series suggest

Table 8.2.—BLOCKING BY INDOLE DERIVATIVES AND HALLUCINOGENIC AGENTS OF ANTIGENIC DETERMINANT OF ENCEPHALITOGENIC PROTEIN IN REACTION WITH LYMPHOCYTES FROM PATIENTS WITH DEGENERATIVE NEUROLOGICAL DISEASES (after Carnegie and others, 1972).

Drug	Relative Molar Ability to block Antigenicity*
5-HT	1.0
LSD	1.0
N,N-Dimethyltryptamine	0.4
5-Chloro-N,N-dimethyl-tryptamine	0.6
5-Methoxy-N,N-dimethyl-tryptamine	0.4
5-Methoxytryptamine	0.3
Mescaline	0.3
DOM, N,N-dimethyl derivative	0.3
Bufotenin	? (incompletely soluble in incubation mixture)

*The following drugs were inactive: tryptamine, indole, 5-hydroxyindole, N-isopropyltryptamine, dehydrobufotenin, 5-methoxy-N,N-diethyltryptamine, 1-methyl-5-methoxy-N,N-dimethyltryptamine, 5-benzyloxy-N,N-di-n-butyltryptamine, 3-(β -N-piperidinoethyl)indole, 3-(β -N-pyrrolidinoethyl)indole.

that such a structure lacks the features optimal for high hallucinogenic activity (see Chapter 3). A second prediction was that if all three active groups on 5-HT are blocked then the resultant compound should be inactivated because of lack of bonding sites. Thus, 5-methoxy-N,N-dimethyltryptamine, with only two groups blocked, disrupted rat behaviour at 2.5 mg./kg. and is a potent hallucinogen in man, whereas its 1-methyl derivative, with all three active groups blocked, has only a mild stimulant or amphetamine-like action at 10 mg./kg. in the rat.

Smythies and his colleagues (Smythies, Benington, and Morin, 1970) also wished to find out whether the two halves of the LSD molecule were equally effective in contributing to the hallucinogenic properties. They considered that an approximation to the molecule could be achieved with 1-methyl-1,2,5,6-tetrahydropyridine-3-(N,N-diethylcarboxamide) (THPC) and mescaline (Fig. 8.3). It was found

that 15 mg./kg. of THPC given 45 minutes before 12.5 mg./kg. of mescaline markedly potentiated the behavioural effects of the latter in rats. The same dose of THPC given before an equivalent dose of LSD (0.1 mg./kg.) gave no such potentiation; indeed the effects were inhibited. The most likely explanation of this finding was considered to be that mescaline occupied only a half of the LSD site

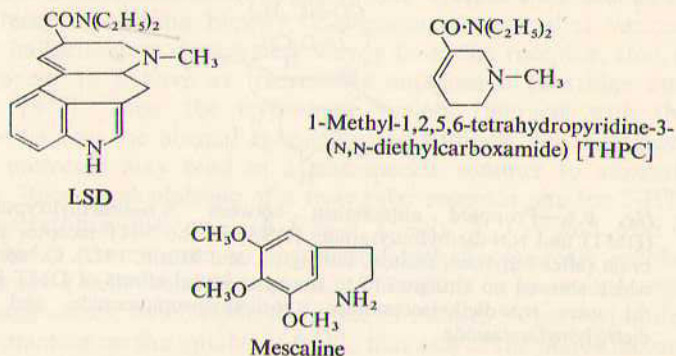


Fig. 8.3.—Drugs used by Smythies, Beaton, Benington, and Morin (1970). Mescaline and THPC are designed to approximate to the two halves of the LSD molecule.

and that occupation of the other half by THPC increased the effect, whereas it would block the binding by LSD; the alternative explanation, that THPC might affect some other brain mechanism and thus potentiate the effect of mescaline on some other system, was considered less likely in view of the lack of potentiation of LSD by THPC.

The same kind of approach was used later by Smythies, Beaton, Benington, and Morin (1972). The purpose of these experiments was to decide whether the whole or only part of the THPC molecule was necessary to block the actions of the hallucinogenic *N,N*-dialkyltryptamines, particularly the dimethyl compound DMT. Four compounds, *N,N*-diethylacetamide, *N,N*-diethylpropionamide, *N,N*-diethylbutyramide (DBA), and *N,N*-diethylvinylacetamide, were first given to rats at 20 mg./kg., when only DBA had any disruptive effect, albeit slight, in its own right. DMT at 10 mg./kg. had a considerable disrupting effect, which was reduced markedly by pre-treatment with DBA but not any of the other THPC fragments. It had been predicted that DBA would exert this inhibitory action, and the suggested explanation was that it filled the receptor site in such a way as to prevent the binding of the side-chain nitrogen of DMT (Fig. 8.4). Since neither mescaline nor DOM would be expected to

occupy that part of the receptor at which the DMT side-chain binds, DBA would not be expected to inhibit the behavioural—presumably hallucinogenic—effects of these phenylalkylamine derivatives. Further experiments confirmed this lack of inhibitory action of DBA.

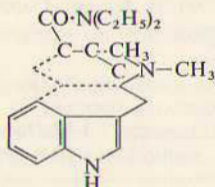


Fig. 8.4.—Proposed antagonism between *N,N*-dimethyltryptamine (DMT) and *N,N*-diethylbutyramide (DBA) at the 5-HT receptor in the brain (after Smythies, Beaton, Benington, and Morin, 1972). Compounds which showed no antagonism to the behavioural effects of DMT in the rat were *N,N*-diethylacetamide, *N,N*-diethylpropionamide, and *N,N*-diethylvinylacetamide.

Leonard and Stonier (1972) also studied the effect of THPC on some pharmacological and neurochemical changes induced in the rat by mescaline. In only two respects did the drug modify the actions of mescaline. It could reverse the effect of mescaline in reserpinized mice which had also been treated with α -methyl-*m*-tyrosine. The latter drug reduces the concentration of brain noradrenaline by forming a false transmitter substance, metaraminol, which displaces noradrenaline from its storage sites (Andén 1964). Secondly, THPC in combination with mescaline potentiated the depletion of brain noradrenaline following the administration of 4, α -dimethyl-*m*-tyramine (H 77/77), a drug reported to displace brain catecholamines (Carlsson, Corrodi, Fuxe, and Hökfelt, 1969). In a good many other neurochemical studies, THPC had no influence on the actions of mescaline and it is not possible to say whether these findings do or do not lend weight to the hypothesis of Smythies and his colleagues. It is probably fair to say, however, that sufficient evidence exists to make it reasonably certain that LSD and related drugs interact with 5-HT receptors in the brain, that is the first stage of the scheme of Freedman and Aghajanian, although there will still be debate over the nature of these receptors.

One major difficulty seems to be to explain why the relatively large LSD molecule appears to fit better to a receptor 'designed' to accommodate the relatively small 5-HT molecule than do, for example, *N,N*-dialkyltryptamines which are much more closely

analogous to 5-HT in size. The argument perhaps narrows down to the question whether LSD acts as an agonist or antagonist at these 5-HT receptors. If it is the latter then there are precedents for large molecules acting as antagonists at receptors where the natural transmitter substance is a relatively small molecule. A good example is atropine, a relatively bulky molecule, acting as a competitive antagonist to acetylcholine at its muscarinic receptor sites. Studies of 5-HT receptors in the blowfly, *Calliphora*, suggest that various indolic hallucinogens detach very slowly from the receptor, that is they appear to behave as irreversible antagonists (Berridge and Prince, 1973). Thus, the tryptamine moiety interacts with the receptor as does the normal agonist but, in addition, the remainder of the molecule may bind in a non-specific manner to adjacent regions. Recent calculations of a triangular receptor site for 5-HT, with interatomic distances of 5.84 Å (N-N), 5.71 Å and 6.96 Å (N-O, N-O), are claimed to accommodate hallucinogenic indolealkylamines (Kelley and Adamson, 1973). This is in accord with other suggestions, based upon the effect of indole, 5-hydroxyindole, and tryptamine on the uptake of 5-HT, that one of the major factors influencing the binding of 5-HT at its receptor site is formation of a Schiff base between the ethylamine side-chain and an appropriate carbonyl residue on the site (Alivisatos, Ungar, Seth, Levitt, Geroulis, and Meyer, 1971). However, this model takes no account of the imino moiety, which is vital to the action of 5-HT, at least in the peripheral nervous system (Pinder, Green, and Thompson, 1971).

Steric and Electronic Factors

The concept implicit in the studies of Smythies and his colleagues is of a rather large and complex receptor area with which a molecule of the hallucinogen may interact at several sites, be it as agonist or antagonist. Their experiments with THPC, which reduces the behavioural effects of LSD but enhances those of mescaline, further suggest that the sites associated with the A and B rings of LSD are related directly to hallucinogenic activity while D ring occupation either modulates reactivity or affects approach to the A-B receptor site. Snyder and Richelson (1968, 1970) have suggested that hallucinogenic activity depends in part upon the degree to which a molecule tends to mimic this ring structure of LSD (Fig. 8.5).

The hallucinogenic potency of indolealkylamines is, however, only partly accounted for by their structural resemblance to LSD. Certainly, psilocin is the tryptamine most likely to assume a stable A-B-C configuration, by intramolecular hydrogen bonding between the terminal amino group and the 4-hydroxyl moiety (Snyder and Merrill, 1965), and it is the most potent hallucinogen of the

series. Bufotenin and 6-hydroxy-*N,N*-dimethyltryptamine, which are unlikely to form ring C, are only weakly hallucinogenic or are inactive. The harmala alkaloids cannot form ring C while the iboga alkaloids contain two cross-linked rings attached to the B ring;

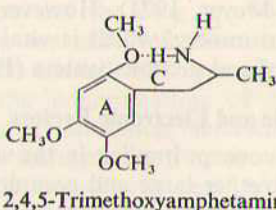
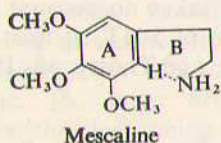
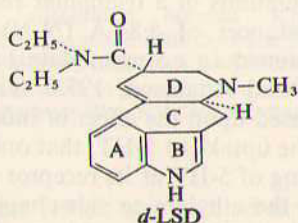
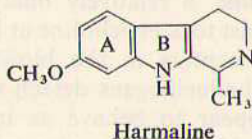
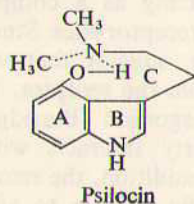


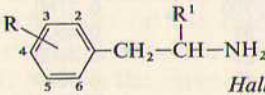
Fig. 8.5.—Structural relationship between LSD and other hallucinogens, showing the degree to which the latter can mimic the ring structure of LSD by hydrogen bond formation.

neither group fits easily into the scheme and they appear to have only weak activity. Nevertheless, compounds which are unlikely to assume the A-B-C configuration also include the hallucinogenic compounds *N,N*-dimethyl- and *N,N*-diethyl-tryptamine, and 5-methoxy-*N,N*-dimethyltryptamine which has been quoted as being equipotent or more potent than psilocin.

Extension of the Snyder theory to phenylalkylamines suggests that B ring formation requires hydrogen atoms at ring positions 2 and 6, or a hydrogen at position 2 with a 6-methoxy sterically hindered by another methoxy group at position 5. In the latter case the

5-methoxy group hinders rotation of the 6-methoxy into a plane favourable for C-ring formation. The latter process requires a methoxy group at 2 or 6; a methylenedioxy group at 3,4 offers less steric hindrance to the 2-methoxy group than a methoxy group at the 3-position. Table 8.3 suggests that compounds that can form ring C have higher potencies than those which are likely to form ring B, though there is considerable variation in potency and structure, and

Table 8.3.—PHENYLALKYLAMINES: RELATIONSHIPS BETWEEN STRUCTURE, HALLUCINOGENIC POTENCY, AND OTHER PARAMETERS.

Compound*	R	R'			
			Hallucino- genic Potency (<i>man, mesca- line units</i>)	Possible LSD ring	E _H
Amphetamine	H	H	0	B	0.5885
Mescaline	3,4,5-(OCH ₃) ₃	H	1.0	B	0.5226
TMA	3,4,5-(OCH ₃) ₃	CH ₃	2	B	0.5218
TMA-4	2,3,5-(OCH ₃) ₃	CH ₃	4	B	0.5026
TMA-3	2,3,4-(OCH ₃) ₃	CH ₃	< 2	B	0.5274
MMDA-3a	2-OCH ₃ -3,4-OCH ₂ O	CH ₃	10	C	—
TMA-6	2,4,6-(OCH ₃) ₃	CH ₃	10	C	0.5217
TMA-5	2,3,6-(OCH ₃) ₃	CH ₃	13	C	0.5112
TMA-2	2,4,5-(OCH ₃) ₃	CH ₃	17	C	0.5001
2,5-DMA	2,5-(OCH ₃) ₂	CH ₃	8	C	0.5012
2,4-DMA	2,4-(OCH ₃) ₂	CH ₃	5	C	0.5194
3,4-DMA	3,4-(OCH ₃) ₂	CH ₃	< 1	B	0.5238
PMA	4-OCH ₃	CH ₃	5	B	0.5262
3,4-MDA	3,4-OCH ₂ O	CH ₃	3	B	—
DOM	2,5-(OCH ₃) ₂ -4-CH ₃	CH ₃	80	C	0.4929

*Abbreviations used are: TMA, Trimethoxyamphetamine; MMDA, Methoxy-methylenedioxy-amphetamine; DMA, Dimethoxyamphetamine; PMA, *p*-Methoxyamphetamine; MDA, Methylenedioxyamphetamine; DOM, 2,5-Dimethoxy-4-methylamphetamine.

critics have pointed out that B ring formation from a phenylalkylamine gives a 6- rather than the desired 5-membered ring of the indoles (*see* Snyder and Richelson, 1970). Furthermore, while the theory does offer an explanation for the necessity for hallucinogenic properties of 2,5-dimethoxy substitution in the phenylalkylamines, it fails to accommodate such active compounds as the 2-phenylcyclopropylamines which are sterically prevented from forming either ring B or C. It is also clear that the *actual* molecular structures of LSD, psilocin (as psilocybin), and 2,4,5-trimethoxyamphetamine,

as well as those of other amphetamines, as determined by X-ray crystallography, do not correspond to those *proposed* by Snyder, though conformations may be different in solution at the receptor from those which prevail in the solid state (Chothia and Pauling, 1969; Baker, Chothia, Pauling, and Weber, 1973).

Table 8.4.—ENERGY CALCULATIONS FOR SOME HALLUCINOGENS (from Snyder and Merrill, 1965; Kang and Green, 1970).

Compound*	Hallucinogenic Potency (man, mescaline units)	$E_H^\dagger$	Largest Negative Pi charge‡	Super- delocaliza- bility§
LSD	3700	0.2180	?	?
Psilocin	31	0.4603	-0.0770	-1.53
6-OHDET	25	0.4700	-0.0800	-1.53
TMA-2	17	0.4810 (0.5001)	-0.0854	+1.14
Bufotenin	?	0.5147	-0.0840	-1.43
DMT, DET	4	0.5164	-0.0810	-1.43
TMA	2.2	0.5357 (0.5218)	-0.1040	+1.23
TMA-3	2	0.5696 (0.5274)	-0.0716	+1.05
Mescaline	1	0.5357 (0.5226)	-0.1040	+1.23

*Abbreviations used: LSD, Lysergic acid diethylamide; OH, Hydroxyl; DET, Diethyltryptamine; DMT, Dimethyltryptamine; TMA, Trimethoxyamphetamine.

† E_H , the energy of the highest occupied molecular orbital (HOMO), is a relative measure of the ability of an electron in the HOMO of a compound to be transferred to an acceptor molecule, expressed in negative energy (*beta*) units. Thus, LSD is a better electron donor than psilocin.

‡Pi charge represents the net positive or negative charge measured at each atom of the molecule.

§Superdelocalizability is a measure, in reciprocal *beta* units, of the ability of each atom in a molecule to form a weak *pi* bond with an incoming reagent when the *pi* system is unperturbed.

Snyder and Merrill (1965) also studied a number of other molecular parameters of hallucinogenic compounds. They calculated *pi* charge, free valency, superdelocalizability, and energy of the highest occupied molecular orbital (HOMO energy, E_H), and found that high potency correlated with high HOMO energy but not with other parameters (Table 8.4). HOMO energy is a relative measure of electron-donating capacity, and Snyder and Merrill concluded that drug-receptor interaction for these compounds involves electron donation. Thus, reduction of the C-9:C-10 double bond of LSD, or hydration (giving lumi-LSD), or bromine substitution at C-2 (giving BOL-148), would markedly diminish electron donation and

also potency. Kang and Green (1970) have also calculated E_H for a large group of amphetamines (Table 8.3). The relationship between electron donation and hallucinogenic potency is also confirmed by studies of the relative ease of formation of molecular complexes with electron acceptors (Sung and Parker, 1972), or of the u.v. and fluorescent spectral properties of the molecules (Antun, Smythies, Benington, Morin, Barfknecht, and Nichols, 1971; Bailey and Verner, 1972), both of which are functions of the π electron system.

Brawley and Duffield (1972) have plotted E_H against the logarithm of potency for the hallucinogenic amphetamines of Table 8.3 and claim to demonstrate a linear relationship between the two for three separate groups of compounds: (a) the three trimethoxyamphetamines which can form ring C; (b) the three trimethoxyamphetamines which can form ring B; and (c) the three dimethoxyamphetamines which can form either ring. Thus, potency is determined partly by electron-donating capacity and partly by preferred ring formation, though Brawley and Duffield do suggest that their analysis of the Snyder theory still does not account fully for all the potency variations. One can only conclude with them: 'We appear to be far away from a general theory of structure-activity relationships for the psychotomimetics'.

Can we reasonably expect such relationships to exist? Receptor morphology for hallucinogens is unknown, and many other factors are involved at the receptor besides structural compatibility, such as Van der Waal's forces, hydrogen bonding, electron donation, and possibly chemical reaction. Binding and reaction at the receptor are likely to depend upon relations between the site and adjacent structures, and upon the configuration of the approach space to the receptor. Finally, our knowledge of hallucinogenic potencies is what prevails in the whole animal, where factors such as absorption, transport, and metabolism play such an important role that structural considerations *per se* become of almost secondary interest. Certainly, a recent comprehensive analysis of quantum chemical factors in the indolealkylamines suggests that there is little or no correlation with biological activity except for one parameter, the total orbital energy (Kumbar and Sankar, 1973). Theories such as that of Snyder and Richelson seem doomed at best to only partial success until drug-receptor interactions for hallucinogens can be studied in intact cells and systems.

4. ACTION OF HALLUCINOGENS AT 5-HT RECEPTORS

Some evidence has already been presented which indicates an antagonistic action for LSD at 5-HT receptors. Farrow and Van

Vunakis (1972) measured the binding of generally labelled ^3H -LSD to tissue fractions from rat brain and found high affinity LSD binding sites in synaptosomes but not in myelin or mitochondria. The effect of various compounds (all at 10^{-6}M) on the binding of $5.4 \times 10^{-9}\text{M}$ ^3H -LSD to synaptosomes was then measured. It was found that 5-HT, noradrenaline, and tryptamine all inhibited binding as did a number of hallucinogenic drugs and ergonovine, a lysergamide derivative. The ratio of inhibitory potency of mescaline:psilocin:LSD was 0.32:32:6400, which compares quite well with the ratio of hallucinogenic potencies in man, 1:32:4500 (Wolbach, Isbell, and Miner, 1962a, b) and suggests that the drugs act at the same synaptic sites.

The work of Vaccari, Vertua, and Furlani (1971) also supports this view that LSD acts as an antagonist at 5-HT receptors. These workers were following up an original suggestion by Woolley and Campbell (1960, 1962) and Woolley and Gommi (1963) that 5-HT, when bound to the receptor, stimulated the transport of extracellular calcium through the cell membrane, thus making smooth muscle contraction possible. Vaccari and his colleagues set out to determine whether it was possible to dissociate calcium transport and muscle contraction from drug-receptor interaction. They measured calcium uptake by rat fundal strips before and after the addition of 5-HT, *d*-amphetamine, and eleoisoisn; muscle contractions were recorded at the same time. The effects of LSD and neuraminidase on these parameters were studied. The first finding was that 5-HT caused a decrease in calcium uptake by the fundal strips although the tissue contracted maximally. This contrasts with the finding by Woolley and his colleagues that 5-HT caused an increase in calcium uptake by uterine smooth muscle. Both *d*-amphetamine and eleoisoisn caused small, non-significant decreases in calcium uptake with maximal contraction of the tissue. Neuraminidase prevented contraction elicited by 5-HT, *d*-amphetamine, and eleoisoisn. This is probably due to the action of the enzyme in hydrolyzing gangliosides, a finding of significance in view of earlier statements by Woolley (1958) and Woolley and Gommi (1964, 1966) emphasizing the importance of gangliosides in the 5-HT receptor. However, it is likely from the work of Vaccari and Vertua (1970) that drug-receptor interaction is not affected but that some subsequent process, probably active transport of calcium to the contractile structures, is modified by neuraminidase. LSD differed from the enzyme in that it blocked contractions elicited by 5-HT and *d*-amphetamine but not eleoisoisn-induced contractions. Additionally it decreased calcium uptake by normal fundal strips and decreased calcium uptake by strips after treatment with 5-HT and *d*-amphetamine. It was concluded,

therefore, that LSD blocked 5-HT (and presumably *d*-amphetamine) receptors so that calcium transport was not initiated. Whether these findings on smooth muscle are of any relevance to the situation in the central nervous system is, of course, open to question, but interesting possibilities exist and should be further investigated.

Evidence in favour of LSD having an agonist action at 5-HT (or tryptamine) receptors is less common and not entirely persuasive. Thus, Martin and Eades (1968) found that tryptamine shared many pharmacological properties with LSD, and also with related hallucinogens, at least in the dog. Later, Martin and Sloan (1970) gave slow infusions of tryptamine hydrochloride to four volunteers in total amounts of 23–277 mg. The drug produced a dose-related increase in blood-pressure, patellar reflex amplitude, and pupillary diameter. Visceral and sensory changes included numbness, tingling sensations, nausea, feelings of warmth and cold, lightheadedness, and alterations in taste, hearing, and vision. 5-HIAA excretion in the urine was significantly decreased, whereas excretion of tryptamine and indole-3-acetic acid was significantly increased. It was concluded that because of the similarity of the effects of LSD and tryptamine in man then one of the modes of action of LSD is through the occupation of tryptamine receptors. The evidence certainly seems to justify this conclusion, but later Martin and Eades (1972) made the specific suggestion, referring back to the earlier papers, that LSD was acting as an agonist at these receptors. The evidence for this seems less powerful. In their 1972 paper they reported that infusions of LSD or tryptamine increased heart-rate, respiratory rate, and pupillary diameter, facilitated the flexor reflex, and evoked the stepping reflex in the chronic spinal dog. Tolerance developed to these effects of LSD and cross-tolerance to the effects of tryptamine. Again it was concluded that LSD and tryptamine have a common mode of action and that the results support the hypothesis that LSD exerts some of its pharmacological effects by acting as an agonist at tryptamine receptors. In addition to the possibility that an antagonistic action is prevailing in these experiments, however, there remains the question of the relevance of these findings to the 5-HT receptor since it is clear that there are distinct tryptamine and 5-HT receptors, at least in the peripheral nervous system (*see* Pinder and others, 1971).

The role of noradrenaline in the action of LSD and related drugs is less clear even than that of 5-HT. The most likely explanation is that both amines are involved. Reasonably direct evidence for blockade of central adrenergic receptors playing some role in hallucinogenesis was observed by Ratcliffe (1971), who showed that mescaline (100 µg./kg., i.p.) and bufotenin (10 µg./kg.) antagonized the

potentiation of amylobarbitone anaesthesia by noradrenaline in mice. Doses of mescaline in excess of 1 mg./kg. effectively reduced the hypothermia resulting from intracerebral injection of noradrenaline. Doses of bufotenin between 10 μ g. and 1 mg./kg. also reduced the hypothermia, though higher doses potentiated it.

5. NEUROCHEMICAL EFFECTS

The second stage in the Freedman and Aghajanian scheme is the disappearance of LSD from the brain. That this occurs fairly rapidly is indicated by the absorption and metabolism studies described in Chapter 4. In the rat, for example, an intravenous dose of 1.7 μ g./kg. of LSD penetrates the brain within 5 minutes, reaches maximum concentration in 15 minutes, and has disappeared after 1 hour (Diab, Freedman, and Roth, 1971). Rodents, however, deal with the drug at a higher rate than other species which have been studied; the half-life of LSD in rodents is less than 10 minutes whereas in man it disappears from the plasma with a half-life of 109 minutes (Wagner, Aghajanian, and Bing, 1968). Figures for the rate of disappearance of the drug from the human brain are, of course, not available but it seems likely that this occurs fairly rapidly.

According to the Freedman-Aghajanian concept, concurrent with the disappearance of LSD from the brain there is a release or utilization of noradrenaline and a binding of 5-HT. Since the original observation by Freedman (1961) that LSD produced an increase in the levels of brain 5-HT and a decrease in the level of noradrenaline there have been several other studies which confirm this result. One interesting report was by Tonge and Leonard (1969), who measured the effects of four structurally dissimilar hallucinogens upon the metabolism of 5-HT in the brain of rats. The drugs used were LSD (200 μ g./kg., i.p.), the phenylalkylamine mescaline (10 mg./kg.), the antiacetylcholine drug Ditrane (4 mg./kg.), and phencyclidine (10 mg./kg.), the last-named being related to the antiacetylcholine drugs. The particular doses were chosen since they had been shown consistently to produce behavioural changes such as excitement and stereotyped movements. All the drugs produced marked rises in brain 5-HT levels with the maximal rise corresponding well to the peak of behavioural effects. In the early stages of the action of the drugs there were decreases in levels of the 5-HT metabolite 5-HIAA. Neither phencyclidine nor Ditrane had any influence on the activity of aromatic amino-acid decarboxylase (consumed in the synthesis of 5-HT) or of monoamine oxidase (consumed in the degradation of 5-HT). This suggests that the release of 5-HT was being affected and experiments indicated that

the depletion of the amine which follows administration of reserpine or *p*-chlorophenylalanine was reduced by all four drugs. These results seemed to support the contention of Freedman and his colleagues that LSD alters the capacity of tissues to bind 5-HT. It also seems possible that this effect is involved in hallucinogenesis in general. The precise nature of the involvement is, however, difficult to assess. The drugs used in this study possess different basic pharmacological actions and it may be that, as the authors suggest, they act in different ways to produce the same net neurochemical changes. There is also the point that the doses used were very high and although there is clear evidence that the rat is very resistant to the effects of LSD, and possibly of the other drugs, it is also true that recognizable behavioural changes occur following considerably lower doses than those used by Tonge and Leonard. In a subsequent paper (Tonge and Leonard, 1970) they explored the possibility that the changes in the concentrations of brain monoamines might be secondary to effects on their precursors; the results are summarized in Table 8.5.

Table 8.5.—SUMMARY OF THE CHANGES IN BRAIN AND PLASMA CONCENTRATIONS OF TRYPTOPHAN AND TYROSINE IN RATS AFTER INTRAPERITONEAL INJECTIONS OF HALLUCINOGENS (after Tonge and Leonard, 1970)

Parameter	Phencyclidine (3 mg./kg.)	Ditran (2 mg./kg.)	Mescaline (5 mg./kg.)	LSD (100 µg./kg.)
Brain tryptophan	—	—	—	+
Plasma tryptophan	—	—	—	—
Brain tyrosine	+	+	+	+
Plasma tyrosine	—	—	—	—

+, Signifies increased concentration; —, Signifies decreased concentration.

All the drugs, except LSD, caused a depletion of tryptophan from the brain of the rat whereas all produced elevated levels of brain tyrosine. It can be seen that the doses required to produce these effects are lower than those needed to produce the changes in levels of monoamines reported above. The authors noted that the depletion of tryptophan persisted during the period when behavioural effects were most intense. It was speculated that the decreased concentrations of tryptophan found in both brain and plasma might reflect an increased conversion of the amino-acid to 5-HT. Greater amounts of the latter would be available then for storage in the brain. Alternatively, decreased levels of tryptophan might inhibit the release of 5-HT. If less tryptophan were available then 5-HT might be retained in greater amounts in the bound form. The elevation of brain tryptophan by LSD is a finding which cannot be

explained. It was suggested that the elevated brain tyrosine levels might result from a feedback inhibition of tyrosine hydroxylase by free noradrenaline since there is, as has been mentioned above, an increased release of this amine after administration of LSD and other hallucinogens. An alternative explanation is that both the increased brain levels and the decreased plasma levels of tyrosine might simply reflect an increased turnover of noradrenaline with increased uptake of tyrosine from the blood into the brain.

Another hallucinogenic drug studied by Leonard (1972a; 1973) was DOM. Its effects on brain amines were identical to those of LSD in that it reduced the brain concentration of noradrenaline and elevated that of 5-HT. The drug increased the rate of incorporation of tritiated tyrosine into noradrenaline but reduced the rate of incorporation of tryptophan into 5-HT. It also reduced the depletion of brain 5-HT which followed the administration of *p*-chlorophenylalanine. Once again the results suggested that this amphetamine derivative, like several other hallucinogens, increased the turnover of noradrenaline while reducing that of 5-HT. These findings by Leonard, however, are not confirmed by the study of Idänpään-Heikkilä and McIsaac (1970), who found that a dose-level of 10 mg./kg. of DOM given by intraperitoneal injection did not cause any significant change in the levels of brain amines in mice. After 50 mg./kg. brain noradrenaline was increased by 22.5 per cent one hour after injection, while 5-HT was increased by only 5 per cent. This is possibly a species difference since Leonard was using rats, though it may be due to the different dose-levels used. Thus, Leonard used doses of 60 mg./kg., considerably higher than those necessary for the production of behavioural effects and greater than those in the other study.

In an attempt to distinguish between the profiles of biochemical action of stimulant and hallucinogenic amphetamines, Leonard (1972b) compared the effects of *d*-amphetamine, *d*-N-methylamphetamine, *p*-nitro-N-methylamphetamine, and *p*-bromo-N-methylamphetamine, the last three having been reported to be hallucinogenic in animals by Knoll (1970). All four drugs increased the turnover of 5-HT but not, it seemed, by the same mechanism since N-methylamphetamine and its nitro derivative potentiated the effect of 4-methyl- α -ethyl-*m*-tyramine (H 75/12) in depleting brain 5-HT but the other two drugs had no such effect. Methylamphetamine and the 4-nitro compound also decreased the turnover of brain noradrenaline, but again the other drugs lacked this effect. Changes in regional brain levels of noradrenaline, dopamine, 5-HT, normetanephrine, and 5-HIAA were also studied, *p*-bromo-N-methylamphetamine seems to be unique in that it affected the

normetanephrine and 5-HIAA content of the middle brain region. The other drugs affected the metabolism of biogenic amines in at least two of the three brain regions studied. It is apparent that none of these drugs possesses the spectrum of activity characteristic of hallucinogenic indolealkylamines and phenylalkylamines in that they did not increase the turnover of noradrenaline and decrease that of 5-HT; indeed, the tendency was for the reverse to take place. It seemed that potency in decreasing the turnover of noradrenaline correlated with potency in increasing motor activity, for *p*-bromo-*N*-methylamphetamine produces only slight behavioural stimulation even at high doses. Its profile of pharmacological activity in experimental animals was said by Knoll (1970) to be similar to that of LSD, but final assessment of the significance of these behavioural changes and biochemical changes in hallucinogenesis must await careful testing of this and other compounds in man.

p-Methoxyamphetamine was claimed by Shulgin, Sargent, and Naranjo (1969) to show moderate activity in man as a hallucinogen. A study of the biochemical and behavioural effects of this drug compared its action with that of the non-hallucinogenic amphetamine (Hitzemann, Loh, and Domino, 1971). The results are summarized in Table 8.6. One of the more interesting findings was that, like LSD and other hallucinogenic indolealkylamines, *p*-methoxyamphetamine caused an increase in brain 5-HT levels and a reduction in 5-HIAA levels. However, *d*-amphetamine had an identical action. In situations like this, where dynamic processes are involved, it would be unwise to draw far-reaching conclusions from single determinations of amine levels at set times after a single dose or a limited number of doses of a drug. It is perhaps more relevant to note that the profile of biochemical activity of *d*-amphetamine and its *p*-methoxy derivative were not identical in every respect. A significant point is that the large dose of *p*-methoxyamphetamine, the only one with an effect on psychomotor activity, was the only one which produced biochemical effects closely similar to those of *d*-amphetamine. It is possible that the hallucinogenic biochemical profile is that of the lower doses of the drug, while that of the highest dose reflects amphetamine-like activity.

6. RELATIONSHIPS BETWEEN NEUROCHEMICAL CHANGES AND NEUROPHARMACOLOGY

In summary, most of the evidence which has emerged since 1966 lends support to the mode of action of LSD proposed that year by Freedman and Aghajanian, that is that interactions with the 5-HT receptor are the primary action of the drug and that the observed changes in

Table 8.6.—A SUMMARY OF THE BIOCHEMICAL AND BEHAVIOURAL EFFECTS ON MICE OF *p*-METHOXYAMPHETAMINE AND *d*-AMPHETAMINE (after Hitzemann and others, 1971)

Compound and Dose	Levels of Brain Amines and Metabolites				Effects on Accumulation of ^{14}C -DA and ^{14}C -NA from ^{14}C -Tyrosine and ^{14}C -Dopa						Effects on Formation of ^{14}C -Amine Metabolites from ^{14}C -Tyrosine				Effect on psychomotor performance
					Tyrosine		Dopa		NM	3-MT	DOPAC	DOMA			
DA	NA	DA	NA												
PMA 3 mg./kg.	0	0	+	—	—	0	+	+	0	—	0	—	0		
PMA 10 mg./kg.	0	0	+	—	—	+	+	+	0	—	0	—	0		
PMA 30 mg./kg.	—	—	+	—	—	+	+	+	0	—	0	—	+		
<i>d</i> -Amphet- amine 10 mg./ kg.	—	—	+	—	—	0	+	+	0	—	0	—	+		

Abbreviations used: 0, No significant effect; +, Significant increase in concentration or rate; —, Significant decrease in concentration or rate; DA, Dopamine; DOMA, 3,4-Dihydroxymandelic acid; DOPAC, 3,4-Dihydroxyphenylacetic acid; 5-HT, 5-Hydroxytryptamine; 5-HIAA, 5-Hydroxyindole-3-acetic acid; 3-MT, 3-Methoxytyramine; NA, Noradrenaline; NM, Normetanephrine; PMA, *p*-Methoxyamphetamine.

metabolism of brain amines are secondary phenomena. Other biochemical changes attributed to the action of hallucinogens, particularly LSD, such as the effects on brain pseudocholinesterase levels (Thompson, Tickner, and Webster, 1955), are so contradictory that they appear to offer little insight into the mode of action of the drugs (Giarman and Freedman, 1965; Hoffer and Osmond, 1967; Brown, 1972; *see* Chapter 4). Nevertheless, a large number of questions remains unanswered. It is still not clear whether LSD is acting as an agonist or as an antagonist, neither is it clear whether the drug has direct or indirect presynaptic actions, and, most important of all, the ways in which the drug-receptor interaction and the biochemical changes are translated into neurological and behavioural phenomena are very uncertain.

If, as suggested, the main primary action of LSD is an interaction with the receptor for a putative chemical transmitter substance then this, in physiological terms, might be expected to modify synaptic transmission. Thus, many neurophysiological and neuropharmacological studies with this and related drugs have been directed towards elucidating such modifications in synaptic transmission, especially so far as they produce the phenomenon of arousal or affect transmission in specific sensory pathways.

The Arousing Effect of Hallucinogens

A large number of hallucinogenic drugs of the sympathomimetic amine type have been shown to produce 'arousal', that is behavioural alertness accompanied by low-amplitude, high-frequency, desynchronized activity in the E.E.G. recorded from all cortical areas. This finding applies to man as well as to conscious and anaesthetized animals of many species. The drugs reported to produce the effect include, as well as LSD, *N*-methylamphetamine, amphetamine, *p*-methoxyamphetamine, various tri- and di-methoxyamphetamines (Fujimori and Himwich, 1969); mescaline, adrenochrome, and bufotenin (Monnier and Krupp, 1960); psilocybin, psilocin, and *N,N*-dimethyltryptamine (Brodey, Steiner, and Himwich, 1963). Other workers have reported either no consistent effects with LSD (Killam and Killam, 1956) or, especially after relatively large doses of 150–200 µg./kg., high-amplitude, low-frequency waves in the E.E.G. (Adey, Porter, Walter, and Brown, 1965; Chatelier and Borenstein, 1968; Lindsley, Carpenter, Killam, and Killam, 1968). This pattern of E.E.G. activity is probably due in part to the high doses, but may also be a function of the particular environment in which the experiment was conducted. Bradley and Key (1963), for example, found that after 5 µg./kg. of LSD the E.E.G.-activating effect depends upon a minimum amount of stimulation from the

environment. This is in contrast to amphetamine, which produces E.E.G.-activation irrespective of environmental stimulation (Bradley and Elkes, 1957). This, then, discriminates between the alerting produced by hallucinogens and non-hallucinogens, and it was later shown by Bradley and Key (1958) that while amphetamine acts directly on the brain-stem reticular formation to produce alerting, LSD has no such direct action but facilitates input into the reticular formation via afferent collateral pathways. This conclusion emanated in part from studies by Bradley and Elkes (1957) in which the effects of drugs were studied on cats with transections of the brain-stem at various levels. Essentially, in *cerveau isolé* preparations, sectioned at the intercollicular level, neither 20 mg./kg. of amphetamine nor 300 µg./kg. of LSD evoked E.E.G. alerting, but in *encéphale isolé* preparations, sectioned at the C₁ level, amphetamine produced its usual alerting effect while LSD did not; that is the latter drug was dependent on the intactness of the spinal afferent connexions. Subsequently, Bradley and Marley (1965) studied the actions on the central nervous system of cats of tryptamine itself and some N- and α-alkyltryptamines, some of which at least are hallucinogenic agents. Initially, they produced typical 'LSD-like' effects with behavioural arousal accompanied by an alert pattern in the E.E.G. Soon, however, the pattern of electrocortical activity changed to one of predominantly slow waves. This appeared to be due to a depressant action of the drugs on the brain-stem reticular formation.

Results differing somewhat from those of Bradley and Elkes were obtained by Takagi, Yamamoto, Takaor, and Ogiu (1958), who found that in the cat *encéphale isolé* preparation doses of LSD of 50 µg. intravenously or 5 µg./kg. intraventricularly produced electrocortical alerting. Similarly, Schweigerdt and Himwich (1966) found that LSD had an alerting effect on the rabbit *encéphale isolé* preparation, although this effect was abolished by precollicular and postcollicular section. This was in comparison with the non-hallucinogenic *d*-lysergic acid monoethylamide which still produced E.E.G. activation after postcollicular section. In the same way the hallucinogens *p*-methoxyamphetamine, 3,4,5-trimethoxyamphetamine, and DOM activated the E.E.G. only if brain section had been caudal to the medulla, whereas the non-hallucinogenic 3,4-dimethoxyamphetamine still produced some alerting when the section was pretrigeminal (Fujimori and Himwich, 1969). Again, Schweigerdt and Himwich (1964) found that in rabbits sections at the C₁ level removed the alerting effect of bufotenin but not that of 5-HTP, the non-hallucinogenic precursor of 5-HT which produced alerting as long as the section was caudal to the midbrain. Finally, Brodey, and others (1963) found that psilocin, psilocybin, and

N,N-dimethyltryptamine all failed to produce electrocortical alerting in animals sectioned rostral to the medulla.

So, despite detailed differences in the findings, it seems clear that all hallucinogenic sympathomimetic amines produce electrocortical alerting but only if spinal afferent connexions are intact. Their potencies in producing this effect seem to correlate reasonably well with their hallucinogenic potencies. It was pointed out by Brawley and Duffield (1972) that this evidence is compatible with the theory that the behavioural and electrophysiological effects of these drugs are due to actions on sensory systems, especially on sensory collaterals to the reticular formation—that is, the view expressed by Bradley and Key (1963) and by Key (1965a, b). Equally well, the evidence could support the theory, already discussed in this Chapter, that the drugs act on 5-HT-containing neurons, or more probably on 5-HT synapses, in the lower brain-stem. It is claimed by the protagonists of this latter theory that most of the 5-HT-containing neurons in the brain (with the exception of those in the pineal) are in the raphe nuclei of the pons and medulla with many of their terminals in the medulla, pons, and spinal cord. Thus, if the primary action of the hallucinogens is on 5-HT neurons or synapses it would be expected that brain sections at the levels indicated above would prevent the behavioural and neurophysiological consequences of this action.

Neither theory, however, seems to fit all the available facts. As far as the Bradley and Key theory is concerned, it was pointed out by Weil-Malherbe and Szára (1971) that electrocortical arousal is not only dependent on the brain-stem reticular activating system but also upon an interaction between both specific and non-specific neural systems. Thus, the midline thalamic reticular system (Sharpless and Jasper, 1956; Jasper, 1960) seems to be involved, particularly with brief and highly focused cortical arousal and probably subserves attention to particular aspects of the environment (Schlag and Chaillet, 1963). A second arousal system, mainly involving limbic structures and the medial forebrain bundle, was proposed by Roultenberg (1968). It seems clear that the limbic system subserves arousal processes related to basic drives including hunger, thirst, sex, and emotional expression (Maclean, 1949, 1958; Grastyan, 1959; Grossman, 1967). There is a fair amount of evidence to suggest some involvement of the limbic structures in drug-induced hallucinations. The most direct support comes from Baldwin, Lewis, and Frost (1957), who found that LSD was devoid of behavioural effects in monkeys after temporal lobectomy. Additionally, a number of groups of workers have reported slow-wave activity, especially in the hippocampal region, in response to LSD and other hallucinogens.

For example, Schwarz, Sem-Jacobsen, and Petersen (1956) reported 2-7 Hz rhythms in temporal E.E.G. after administration of LSD or mescaline, and Adey, Dennis, and Bell (1962) found 4-5 Hz 'seizures' in the hippocampus of cats after 25 µg./kg. of LSD. Activity of the same frequency was recorded from cortical area 17, the rostral midbrain and the anterior ventral nucleus of the thalamus, providing the animal was kept in the dark and in quiet surroundings. This seems to indicate that the effects of sympathomimetic hallucinogens on limbic structures as well as on the brain-stem reticular formation are dependent upon sensory input. Perhaps one of the most interesting and important pieces of work was that by Fairchild, Alles, Jenden, and Mickey (1967), who compared the effects in the cat of amphetamine, mescaline, and various ring-substituted amphetamines. The alterations in frequency distribution of spontaneous brain electrical activity was measured, and two orthogonal patterns of frequency changes were found which were correlated with dosage of the test compounds. The authors proposed that one of the patterns (low-voltage, high-frequency activity) represented central alerting in the cat while the other (3-10 Hz rhythms in the amygdala, supra-optic nucleus of the hypothalamus, dorsomedial nucleus of the thalamus, caudate nucleus, midbrain reticular formation, and hippocampus) was a correlate of the hallucinogenic activity in man of some of the drugs. Amphetamine produced low-amplitude, high-frequency activity in both cortical and subcortical regions but the proven hallucinogens 3,4,5-trimethoxyamphetamine, 3,4-methylenedioxyamphetamine, and 3,4-methylenedioxy-5-methoxyamphetamine were all more potent than mescaline in producing the 'hallucinogenic effect'. One finding at variance with most of the others is that of Passouant, Passouant-Fontaine, and Cadilhac (1956), who found no effect on hippocampal activity in cats of doses of 50-200 µg./kg. of LSD, though they did record long bursts of 3-4 Hz activity from the hypothalamus and septal area as well as the cerebral cortex. The majority of investigators, however, have found changes in electrical activity of the hippocampus, amygdala, and septal regions in response to LSD and similar drugs. Since these brain areas seem to be involved in attentional, arousal, memorial, and affective functions (Brawley and Duffield, 1972) it is tempting to conclude that the changes have some significance in the effects of the drugs, but much more work is needed before this can be stated with certainty.

The second reservation to the Bradley and Key theory of drug-induced hallucinogenesis is based on the fact that not all investigators agree that sympathomimetic hallucinogens, in contrast to amphetamine, have no direct action on the brain-stem reticular

formation, a concept basic to the theory. For example, Monnier and Krupp (1960) reported that LSD, mescaline, adrenochrome, cocaine, and bufotenin, all enhanced the alerting effects of stimulation of the reticular formation; similarly, Rinaldi and Himwich (1955) found that the threshold stimulus of the midbrain required to produce electrocortical activation in the curarized rabbit was reduced after 1–5 $\mu\text{g./kg.}$ of LSD (i.v.). Other workers (for example, Killam and Killam, 1956) have reported results to support the Bradley and Key theory. It is not possible at present to account for the apparent discrepancies.

The second theory, that LSD acts primarily on 5-HT neurons or synapses in the raphe nuclei, seems to rest heavily on the assumption that such neurons are concentrated exclusively in these nuclei. Demonstrably, this does not seem to be the case, for in the study by Boakes and his colleagues (1970) brain-stem neurons away from the midline, that is certainly outside the raphe, were shown to be excited by iontophoretically applied 5-HT. This excitation could be antagonized by LSD. It is, however, but a minor modification to the theory to assume that the drugs act on neurons in other parts of the lower brain-stem as well as the raphe nuclei. If the action of LSD is one of competitive antagonism to 5-HT then the 5-HT system must be assumed to be inhibitory, the inhibition being removed by LSD resulting in arousal mediated via the brain-stem reticular formation. This is essentially the hypothesis suggested by Brawley and Duffield (1972) and certainly is not seriously at variance with any of the well-documented available facts. The main difficulty remaining is that the neural pathways between the 5-HT neurons in the lower brain-stem and the reticular formation are not well defined.

Other Sensory Systems

It is very probable that as well as modifying input into the reticular formation by way of sensory collaterals, LSD and related drugs also modify transmission in other, more specific, sensory systems. A good deal of electrophysiological evidence is available to support this view but it has not been possible to link the physiological events with modification of synaptic transmission mediated through a specific transmitter substance.

In the visual system the effects of LSD on the retina have been much studied. Very variable results (see Brawley and Duffield, 1972) have been obtained and it is not possible to draw any firm conclusions. Effects of the drug on the optic tract have also been investigated, and perhaps the best studies are those in which single-unit activity has been recorded. Mouriz-Garcia, Schmidt, and Arlazaroff (1969), using curarized cats, found that 14 out of 21 cells

increased their rate of firing by up to 300 per cent after intravenous doses of 50–100 $\mu\text{g./kg.}$ of LSD. However, Brawley and Bradshaw (results quoted by Brawley and Duffield, 1972), using much smaller doses of 5–15 $\mu\text{g./kg.}$, found in the dark-adapted cat that this increase occurred in only 1 of 22 cells. The same cell was similarly responsive to amphetamine, making it doubtful whether this effect is specific for hallucinogens.

The lateral geniculate nucleus, also in the visual pathway, has been much studied. Evarts, Landau, Freygang, and Marshall (1955) found that geniculate transmission in the anaesthetized cat was blocked by an intracarotid dose of 30 $\mu\text{g./kg.}$ of LSD, but transmission within the retina and between geniculate radiation fibres and cortical cells was extremely resistant to inhibition by the drug. Similar results were obtained with bufotenin. When conscious cats were used the dose of LSD required to block geniculate transmission was about 5 times higher (Evarts, 1957). In these conscious animals block of the transmission was associated with a lack of responsiveness to visual stimuli, though they were still fully responsive to sounds. A similar temporary blindness following higher doses of LSD (0.5–1 mg./kg.) has been reported to occur in monkeys (Evarts, 1956). The evidence did not allow conclusions to be drawn concerning the precise mode of action of the hallucinogen in blocking geniculate transmission, that is it was not clear whether it was acting as a competitive antagonist to the synaptic transmitter substance. Later, using iontophoretic techniques, Curtis and Davis (1962, 1963) and Phillis and others (1967) found that LSD blocked the responses of cells in the lateral geniculate nucleus to optic tract stimulation but this was not a specific effect since it was also brought about by dopamine, noradrenaline, adrenaline, BOL-148, tryptamine, and 5-HT. LSD did not antagonize 5-HT effects on these neurons but it did depress responses to acetylcholine and to glutamate. The significance of these findings remains open to question. In particular, it will be necessary to identify the chemical transmitter between the optic tract and lateral geniculate neurons before any clear understanding of drug actions in the nucleus can be formulated.

Effects on the auditory system have received attention. Purpura (1956a,b, 1957) used unanaesthetized cats immobilized with succinylcholine and observed that 2–30 $\mu\text{g./kg.}$ of LSD facilitated the responses on the auditory cortex to click stimuli and on the visual cortex to photic stimuli. Higher doses (40–60 $\mu\text{g./kg.}$), while still facilitating the visual response, depressed the auditory response. These effects could not be obtained in cats anaesthetized with thiopentone. Purpura carried out further experiments in which he

studied the effect of LSD on the cortical potentials evoked by electrical stimulation of the lateral geniculate radiation fibres and of the homolateral suprasylvian gyrus (different points along the visual pathway). From the results of these experiments Purpura concluded that LSD inhibited transmission across axodendritic synapses but facilitated transmission across axosomatic synapses. Brawley and Duffield (1972) do point out, however, that more recent evidence regarding the function of these synapses does not support Purpura's conclusion. Other workers have confirmed his basic findings, but interpretation of observations concerned with evoked potentials is extremely difficult. These potentials vary with the behavioural state, and hence the electrocortical state, of the animal; different methods of recording can also give different results. These studies have not, therefore, contributed much to the understanding of the mode of action of hallucinogens. Nevertheless, Winters and Wallach (1970) did produce a general theory for hallucinogenesis using the E.E.G. and evoked cortical potentials in the cat as measures of the arousal state of the central nervous system in correlations with the behavioural state of the animal. According to these authors there is a continuum of excitatory states of the central nervous system ranging from motor excitation at one extreme to either general anaesthesia or convulsions at the other. Presumably amphetamine acts at one end of this spectrum to produce excitation while the hallucinogenic amphetamines and LSD act at a point in the middle.

7. CONCLUSION

The evidence so far presented is consistent with the view that sympathomimetic hallucinogens interact with 5-HT receptors resulting in a facilitation of input in non-specific and perhaps in specific sensory systems. There remains the problem of explaining how these actions result in the characteristic behavioural effects of the drugs. Any explanation can, at the moment, only be conjectural. It is tempting to conclude, with an oversimplification, that modifications in sensory input result in misinterpretation of the input by decoding mechanisms in the cortex, giving the perceptual disturbances associated with these drugs. A rather more precise explanation for some of the behavioural effects of LSD emerged from ingenious experiments described by Key and Bradley (1960). They used cats with chronically implanted cortical electrodes and conditioned the animals to respond to a sound stimulus by pairing it with an electric shock delivered to the feet. Once the conditioned response was established the animals responded to the sound

stimulus 30 to 40 times without further need for reinforcement. The level of the sound stimulus was gradually decreased during the process of conditioning until it eventually reached a level which appeared to be close to the threshold of hearing for the cat. A dose of LSD (5 $\mu\text{g./kg.}$, i.p.) did not affect the threshold of arousal to a stimulus of a pitch to which the cat had previously been conditioned, but the threshold for a stimulus to which the animal had not been conditioned fell strongly to a level approaching that to which the conditioned animal responded. These experiments indicated that the LSD-treated animals became more sensitive to external stimuli, that is that LSD had increased the level of their significance. Other studies of a rather different type lead to similar conclusions. For example, Ursin (1962) unilaterally stimulated the amygdaloid nuclear complex in cats, producing an attention response directed to the opposite side. The threshold of this response was unaffected by LSD up to 200 $\mu\text{g./kg.}$, suggesting that LSD has no direct action in causing changes in ability to attend to stimuli but rather that the drug interferes with the flow of sensory information into the brain. Key in 1961 reported that LSD reduced the rate of extinction of a conditioned avoidance response in cats, again indicating that the stimulus (auditory) had increased significance for the animals.

Even if these hypotheses concerning the effects of sympathomimetic hallucinogens upon sensory systems are correct it is clear that they only account for part, perhaps a small part, of the syndrome induced by the drugs. Other, more psychological, theories have been propounded but they are beyond the scope of this book; they are summarized briefly by Weil-Malherbe and Szára (1971). It is apparent that much remains to be done before a complete explanation of the mode of action of these drugs emerges, combining the biochemical, behavioural, and psychological features into a unified picture.

II. ANTIACETYLCHOLINE DRUGS

1. ACETYLCHOLINE RECEPTORS

In the peripheral autonomic nervous system antiacetylcholine drugs act as competitive antagonists to acetylcholine at post-ganglionic parasympathetic endings, the so-called 'muscarinic sites'. It is an obvious possibility that drugs of this type which penetrate into the central nervous system produce their behavioural effects by a similar action. For this to be the case it is necessary, in the first instance, for there to be a reasonable certainty that acetylcholine has a function

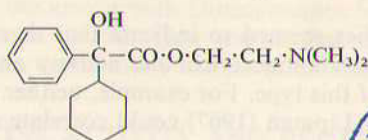
as a chemical neurotransmitter in the central nervous system and that it interacts, at least in some brain areas, with receptors which are analogous to muscarinic receptors in the periphery.

The central neurotransmitter role of acetylcholine is now established beyond all reasonable doubt. The evidence was summarized

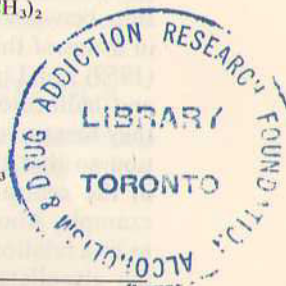
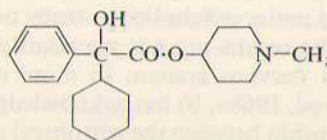
Table 8.7.—PHARMACOLOGICAL ACTIVITIES OF THE RACEMATE AND ENANTIOMERS OF TWO ANTIACETYLCHOLINE DRUGS (after Brimblecombe and others, 1971)

Compound	Enantiomer	Antiacetylcholine Potency on Isolated Guinea-pig Ileum, log K	Potency relative to Atropine in producing Mydriasis in Mice	ED ₅₀ , μmole/kg. for Antagonism of Oxotremorine Effects in Mice	
				Salivation	Tremors
I	Racemate	8.73	0.34	1.40	22.7
	R	9.06	0.76	0.76	5.07
	S	7.07	0.006	> 100	> 100
II	Racemate	10.53	1.17	0.31	3.29
	R	10.29	2.36	0.18	0.56
	S	8.48	0.12	7.75	9.42
Enantiomeric potency ratios:					
I R:I S		100	123	> 100	> 22
II R:II S		272	20	43	38

Compound I



Compound II



by Bradley (1968), who also described studies in which drugs were applied iontophoretically to single neurons in the brain. From these studies it appears that some cholinceptive neurons are specifically responsive to either muscarinic or nicotinic agents. Other evidence for the presence of central muscarinic receptors was given by Bebbington and Brimblecombe (1965). This was based mainly on the fact that muscarinic agents capable of penetrating into the brain, such as oxotremorine and arecoline, give rise to effects such as tremors which are blocked by tertiary amine antiacetylcholine

drugs but not by quaternary ammonium salts of similar pharmacology which cannot cross the blood-brain barrier.

Having established with a reasonable degree of certainty the presence of central muscarinic receptors there remain the questions as to whether hallucinogenic antiacetylcholine drugs interact with these receptors and whether this interaction is responsible for the hallucinogenic effects. Perhaps the best evidence for similar antiacetylcholine drug-receptor interactions peripherally and centrally is provided by studies in the authors' own laboratories in which the relative potencies of enantiomeric pairs of antiacetylcholine drugs have been measured, using a number of test procedures. Some results, reported by Brimblecombe, Green, Inch, and Thompson (1971), are summarized in *Table 8.7* and are discussed in detail, together with other relevant information, by Inch and Brimblecombe (1974). Essentially, the similarity between the peripheral and central enantiomeric potency ratios of the antiacetylcholine drugs is sufficiently close, allowing for effects such as transport and metabolism, to suggest that the central receptors with which they interact are similar to those in the peripheral nervous system.

2. ANTIACETYLCHOLINE AND HALLUCINOGENIC ACTIVITY

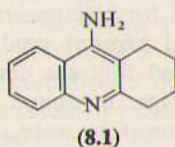
Early studies seemed to indicate that there was no direct relationship between antiacetylcholine activity and hallucinogenic activity in drugs of this type. For example, neither Abood, Ostfeld, and Biel (1959) nor Lipman (1967) could correlate antiacetylcholine potency and hallucinogenic potency in a series of glycollic acid esters, but they measured antiacetylcholine potency on an isolated gut preparation so that the results are not necessarily relevant to the situation in the central nervous system. In more recent papers Abood (for example, Abood, 1968a, b) has acknowledged that there does appear to be a relationship between the peripheral antiacetylcholine action of the glycollate esters and their hallucinogenic efficacy, but he still does not seem to favour the view that a causal relationship exists; in his discussion of structure-activity relationships in compounds of this type he is careful to distinguish between the two types of activity.

Information is now available concerning the central antiacetylcholine potency of a number of drugs, but reliable data on their potency in man are not complete. In the limited number of cases where comparisons are possible there does seem to be a reasonable degree of correlation. The reported hallucinogenic doses of hyoscyne in man range from 0.8 mg. to 4 mg. and of atropine from 30 mg. to 50 mg. (Miller, 1956; White, Rinaldi, and Himwich, 1956;

Ostfeld and Araguette, 1962), that is the ratio of potencies lies between 8 and 60. Recently in a careful comparative study of the two drugs in human volunteers (Ketchum, Sidell, Crowell, Aghajanian, and Hayes, 1973), it was reported that the mean potency ratio was 8.2, based upon ten different effects of the drugs. The corresponding ratios for central antiacetylcholine potencies, based on antagonism of oxotremorine-induced tremors in mice, is about 14 (Brimblecombe and Green, 1968). In 1959 Abood and his colleagues found that *N*-methyl-3-piperidyl benzilate was about twice as potent in man as its *N*-ethyl homologue. Brimblecombe and Green observed that the ratio of central antiacetylcholine potencies for the two compounds was about 1.5 to 1.0. Ketchum's group also included Ditrán in their study on human volunteers and reported it as being 1.3 times as potent as atropine; the corresponding figure given by Brimblecombe and Green is 18, which does not agree well with either these results or with the effective doses for Ditrán reported in other human studies. Wilson and Shagass (1964) found that 0.1 mg./kg. (that is 7–10 mg./man) produced marked psychotic symptoms, giving a ratio of potency to atropine of between 3 and 7. Davis, Ford, Tupin, and Colvin (1964), in another study with Ditrán, used doses of 12.5–135 mg., that is ratios of potencies of between 0.2 and 4. So although the degree of correspondence between the two sets of figures is generally good, the results with Ditrán cannot be ignored. Clearly, many more results of this kind are needed before the significance of any possible correlations can be established.

3. ANTIACETYLCHOLINE ACTIVITY AND BEHAVIOUR

Although there is a lack of direct evidence for a causal relationship between antiacetylcholine actions and hallucinogenic effects, other,



more indirect, evidence exists in support. Firstly, the behavioural effects of antiacetylcholine drugs can be antagonized by administration of anticholinesterase agents. In 1960 Gershon and Olariu reported that tetrahydroaminoacridine (THA **8.1**), which has anticholinesterase activity, specifically antagonized the central as well as the peripheral actions of Ditrán and other glycolic acid esters in man. The hallucinogenic effects of LSD, mescaline, and phencyclidine

were not modified by THA. However, Abood and Biel (1962) and Gershon and Olariu (1960) reported that the organophosphate anticholinesterase dyflos and the carbamate anticholinesterase physostigmine were not effective in antagonizing the overt effects of glycollates in rats or dogs. That this may well be due to a deficiency in the animal testing procedures is indicated by the fact that physostigmine clearly antagonizes the central effects of the glycollate esters in man (Wills, 1964, quoted by Abood, 1968a). Yohimbine, which possesses anticholinesterase activity, has also been reported as being an antagonist to Ditrane (Gershon and Bell, 1963), although it should be noted that yohimbine also has adrenergic blocking properties and both types of activity may be required for effective antagonism.

Other evidence linking behavioural or neuropharmacological activity of antiacetylcholine drugs with their antiacetylcholine activity comes from animal studies. There is, however, a difficulty in interpreting these studies in that it can never be clear whether the particular parameters observed in animals bear any direct relationship to hallucinogenic actions in man.

All centrally acting antiacetylcholine drugs produce a phenomenon usually called 'E.E.G.-behavioural dissociation'. It was first reported by Wikler in 1952, who found that dogs which had received atropine had an E.E.G. pattern normally associated with sleep (high voltage, slow waves), although they could be behaviourally alert. Since this initial observation, other workers have reported this kind of dissociation in other species with a variety of antiacetylcholine drugs. It is possible to quantify the degree of dissociation using a method described by Bradley and Key (1958). The cat *encéphale isolé* preparation (cord sectioned at C₁) is used, and behavioural and electrocortical dissociation can be produced by electrical stimulation of the brain-stem reticular formation. Antiacetylcholine drugs cause an elevation of the threshold for electrocortical arousal but leave the threshold for behavioural arousal unaltered. Brimblecombe and Green (1967, 1968) showed that the central antiacetylcholine potencies of a series of drugs, measured by their ability to block oxotremorine-induced tremors in mice, correlated well with their potencies in elevating the electrocortical arousal thresholds in cat *encéphale isolé* preparations. This seems to provide quantitative evidence for a cholinergic link in the mesodiencephalic activating system which is concerned in electrocortical arousal, but it is not clear what significance this has in terms of behaviour of the animal. Wikler, in his original paper of 1952, concluded that although the systems subserving synchronization and desynchronization of the E.E.G. were normally interlocked with those subserving sleep and

wakefulness, they were distinct and that sleep and wakefulness were not consequences of changes in electrocortical activity. Later, in 1954, Wikler suggested that the E.E.G. systems were also independent of those subserving ideation, mood, level of awareness, motility, and sensation. If this view is correct then the actions of antiacetylcholine drugs on the mesodiencephalic activating system would presumably not influence these psychological parameters.

Many attempts to correlate antiacetylcholine activities of drugs with their activity in modifying certain aspects of animal behaviour have met with mixed success. Centrally acting antiacetylcholine drugs produce marked hyperactivity in animals, and Abood (1968b) found that among a series of piperidyl glycolates their hallucinogenic potency was correlated with their potency in producing hyperactivity in animals. However, though piperazinyl glycolate esters were only weakly hallucinogenic in man they also increased spontaneous activity in animals to a marked degree. Brimblecombe and Buxton (1972) compared the potencies of eight antiacetylcholine drugs in producing increases in the spontaneous activity of rats with various measures of their antiacetylcholine activity, both central and peripheral. While the drugs all produced marked increases in activity there was not a statistically significant correlation between their potencies in this respect and any of the measures of antiacetylcholine potency. It should be recognized, however, that spontaneous motor activity is a relatively complex pattern of behaviour almost certainly not mediated entirely by cholinergic systems, and it may not be surprising that correlations could not be demonstrated.

There have also been many studies of the actions of antiacetylcholine drugs on conditioned behaviour, and many authors have attempted to explain their results in terms of effects on 'learning or memory'. It is not appropriate here to give a detailed account of these studies, and many of them carried out prior to 1966 have been summarized by Longo. The results were confused in that drugs were shown variously to disrupt conditioned behaviour, to have no effect upon it, or to produce increments in performance. One reason for confusion is undoubtedly the hyperactivity produced concomitantly, which might in some situations give a spurious impression of improvements in performance. This is particularly the case in conditioned avoidance situations where the physical nature of the apparatus is such that hyperactivity *per se* might give the animal a better opportunity to acquire true avoidances. In view of the varied nature of the results it is probably unwise at this stage to state firmly that antiacetylcholine drugs disrupt the processes of memory and learning. On the other hand, it does appear that they have amnesic

properties in man and many of the effects observed in animals in conditioning experiments could be explained in terms of retrograde amnesia.

It is very difficult with most behavioural studies to draw any conclusions concerning the mode of action of the drugs in producing the reported changes. It is often assumed, but without any real foundation, that because antiacetylcholine drugs are by definition competitive antagonists of acetylcholine then any behavioural effects observed are due to blocking action at central cholinergic synapses. Perhaps one of the most plausible hypotheses and one backed by considerable experimental evidence is that of Carlton (1963). He considered the results of a number of studies of the effects of antiacetylcholine drugs in operant conditioning situations and suggested that the drugs were giving an increased number of unrewarded responses owing to a disinhibition of the process which normally suppresses them. He speculated that this normal inhibitory process was mediated through muscarinic cholinergic synapses. He also assumed that there was a reciprocal activating system which could be stimulated by amphetamine to produce effects on operant conditioning essentially similar to those produced by antiacetylcholine drugs. In 1968 Carlton developed his hypothesis further to suggest that the drugs attenuated the process of habituation, that is the process whereby the repetition of a stimulus results in the loss of the effect it produced initially. The implication is that this habituation process is acetylcholine-mediated. Further, it is implied that antiacetylcholine drugs modify the processes whereby sensory information is relayed to the central nervous system or processed once it is there. This seems to be in agreement with the findings of Green and Aldous (1972), who, in studies with cats, concluded that antiacetylcholine drugs reduced the significance of external stimuli. This is in contrast with the findings of Key (1965a, b), referred to earlier in this chapter, that LSD seemed to increase the significance of such stimuli.

It appears then that the most likely mode of action of antiacetylcholine drugs in producing their behavioural or hallucinogenic effects is a competitive antagonism of acetylcholine at central muscarinic sites. The evidence is not unequivocal, however, and it is by no means clear how such a pharmacological action is translated into the observed behavioural effects.

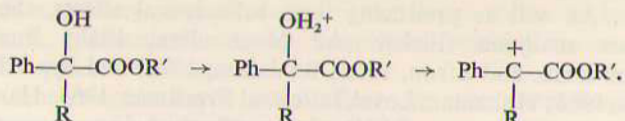
4. OTHER POSSIBLE MECHANISMS OF ACTION

There are other possible, but in our view less likely, explanations of the hallucinogenic mode of action of antiacetylcholine drugs. For

example, it is clear that many antiacetylcholine drugs cause decreases in the total acetylcholine content of the brain. This was first shown by Giarmann and Pepeu (1962), who suggested, as did Giarmann and Freedman (1965), that the hallucinogenic activities of such drugs might be directly related to these alterations in brain acetylcholine levels. It is difficult to obtain direct evidence to test the validity of the suggestion, and it seems likely that the decreased levels of acetylcholine are the consequences of cholinergic blockade resulting from a feedback mechanism. Even if this is the case it does not detract from the view that the decreased acetylcholine levels might be responsible for the behavioural effects of the drugs.

Abood (1968b, 1970) had made a number of suggestions as to the mode of action of hallucinogenic antiacetylcholine drugs. He noted that the partial depolarization of isolated frog sartorius muscles which occurs when they are immersed in calcium-free Ringer's solution could be reversed by the addition of low concentrations of certain glycollate esters to the solution. The implication was that the esters were acting similarly to calcium ions in restoring the resting potential of the muscle. On excited single muscle-fibres the esters also had similar actions to calcium ions, in that they both produced a prolongation of the negative after-potential presumably due to a decreased permeability of the membrane to ions, notably sodium and potassium. These effects on membranes might contribute to the central actions of the glycollates, including their effects on behaviour. Certainly, if as Abood suggests, these drugs irreversibly occupy calcium binding sites this may be expected to produce a nerve-block. The fact that the drugs possess local anaesthetic activity is not incompatible with such a suggestion. However, it seems quite possible that these effects on membranes could be the result of, rather than an alternative to, an interaction with central cholinceptive systems.

Another suggestion made by Abood (1968b) was that the hallucinogenic glycollates produced direct acylation of the receptor by a carbonium ion mechanism:



The formation of such a carbonium ion would destroy the asymmetry of the molecule, and so stereochemical factors would not be expected to influence activity. However, it has been shown by Brimblecombe and others (1971) that there are considerable differences in peripheral and central antiacetylcholine potencies and in

duration of action between the enantiomers of various compounds of this type.

The results obtained by Brimblecombe and his colleagues seem to invalidate another suggestion by Abood that the duration of action of antiacetylcholine drugs is related to their ease of acidic hydrolysis. In fact, as was noted above, pairs of enantiomers with the same rates of hydrolysis possess markedly different durations of action.

Abood also claims that the availability of the non-bonded electron pair on the nitrogen atom is correlated with the hallucinogenic potency of the glycollate esters. It is commonly accepted that quaternary compounds are more potent as antiacetylcholine agents than the corresponding tertiary compounds, so that the contribution of the lone pair to antiacetylcholine activity seems to be of relatively little importance. As far as hallucinogenic activity is concerned perhaps the main effect of the steric environment of these electrons will be to influence the pK_a and hence the degree of protonation at physiological pH of the drugs. This in turn will influence such properties as penetration through various barriers, notably the blood-brain barrier.

In summary, the present authors incline to the view that the hallucinogenic actions of antiacetylcholine drugs are due to their competitive antagonism of acetylcholine at central muscarinic receptors. They feel with Brown (1972) that Abood 'appears, out-of-hand, to reject the hypothesis on the basis that we don't know much about central cholinergic transmission *per se*'.

III. CANNABIS

Very little of value can be written concerning the mode of action of cannabis derivatives. It was pointed out in Chapter 5 that the active principles of the resin have been recognized only in recent years and that much of the earlier work with impure preparations does not contribute very much to our knowledge. Nevertheless, it is clear that cannabinoids exert a depressant action on the central nervous system. As well as producing their behavioural effects, they also produce analgesia (Bicher and Mechoulam, 1968; Buxbaum, Sanders-Bush, and Efron, 1969; Buxbaum, 1972) and hyperthermia (Miras, 1965; Holtzman, Lovel, Jaffe, and Freedman, 1969; Hardman, Domino, and Seevers, 1971), both effects being characteristic of central nervous system depressants as is their potentiation of barbiturate sleeping time (Domino and others, 1971).

Behaviourally, there are indications of central nervous stimulation at low doses but clearly of depression at higher doses (Bose, Saifi, and Bhagwat, 1964; Carlini and Kramer, 1965; Kubena and Barry, 1970).

There have been difficulties in obtaining relationships between doses of cannabinoids and their behavioural responses as a result of the development of tolerance (McMillan, Harris, Frankenheim, and Kennedy, 1970; McMillan, Harris, Turk, and Kennedy, 1970). Tolerance does not extend to all the behavioural effects, however, since Bueno and Carlini (1972) showed that rats became tolerant to the effects on rope-climbing behaviour of daily injections of a marihuana extract but not to its effects on a lever-pressing task. Similarly, Harris, Waters, and McLendon (1972) found that monkeys soon became tolerant to the effects of Δ^9 -THC on avoidance-responding in a lever-pressing situation but not to food-responding in the same situation.

The effects of cannabinoids on the electrical activity of the brain are exactly what are expected of a depressant of the central nervous system. Domino and others (1971) found that intravenous doses of 0.25 mg./kg. of the synthetic cannabinoid DMHP administered to dogs with chronically implanted brain electrodes caused the animals to become drowsy with the concurrent appearance of high-amplitude, low-frequency electrical activity at both cortical and subcortical sites. Both the drowsiness and the electrocortical activity could be reversed by the application of sensory stimuli or by intravenous *d*-amphetamine (0.25 mg./kg.). Similar effects were observed in rhesus monkeys.

The neuropharmacological effects of cannabinoids have been discussed in Chapter 5, and it is sufficient here to summarize the findings. They refer in the main to DMHP, but extrapolation is probably permissible to the natural drugs which have similar pharmacology. The main conclusions are:

1. There is a correlation between the pattern of electrical activity recorded from the brain and the behavioural effects of the drugs.
2. The blockade of conditioned responses by cannabinoids is not due to depression of afferent input or to impairment of motor output but rather to confusional or depressant effects on higher centres in the brain.
3. The primary site of action of the drugs seems to be in the cerebrum, particularly in the secondary association areas and related subcortical structures.
4. Cannabinoids have little effect on the mesodiencephalic activating system unless large doses are given, when the arousal threshold is elevated.
5. Effects on the amygdala are primarily depressant.
6. Slight depressant effects on the spinal cord can be detected, but these do not seem to account for the observed body swaying or depression of the flexor reflex.

7. Large doses of cannabinoids produce exaggerated startle responses which sometimes include convulsive movements. There is no knowledge of the mechanism involved.

A good many attempts have been made to determine whether the behavioural effects of cannabinoids are accompanied by changes in levels of brain amines. The evidence is at present conflicting and no clearcut conclusions can be drawn.

Holtzmann and his colleagues (1969) measured levels of noradrenaline and 5-HT in the brains of mice 45 minutes after the injection (i.p.) of pure Δ^9 -THC. Doses of greater than 5 mg./kg increased whole brain concentrations of 5-HT with significant increases following doses of 10, 100, 200, and 500 mg./kg. Significant decreases in noradrenaline levels were found after 5 and 10 mg./kg. but increases with the higher doses. The time-course of the changes in amine concentrations seemed to correspond to that of hypothermia in the animals. It was noted that while LSD and amphetamine also cause reductions in brain noradrenaline and increases in brain 5-HT levels, the animals after these drugs are behaviourally alert and hyperactive rather than hypoactive. Another difference was that no changes in levels of the 5-HT metabolite 5-HIAA could be detected in animals which had been given Δ^9 -THC whereas its levels were decreased after administration of LSD. Pal and Ghosh (1972) also studied the urinary excretion of 5-HIAA in rats after doses of 10–100 mg./kg. of Δ^9 -THC. Significant increases in its concentration were found after repeated doses at the lower level or a single dose of 100 mg./kg.

Schildkraut and Efron (1971) found only very small increases in brain 5-HT levels and very small decreases in noradrenaline levels after giving 80 mg./kg. of Δ^9 -THC to rats. The rate of disappearance from the brain of tritiated noradrenaline injected intracisternally was accelerated and there was a small increase in its uptake in the brain. These effects may be specific, but it is also possible that they are indirect and mediated through stress or hypothermia. Ho, Taylor, Englert, and McIsaac (1971) administered Δ^9 -THC to rats by inhalation from cigarettes. They assayed whole brain for noradrenaline and 5-HT, and their metabolites normetanephrine and 5-HIAA. Repeated inhalation of the drug did not affect levels of noradrenaline or 5-HT, but there were decreases in the concentrations of both metabolites possibly due to an increased rate of their transport from the brain.

The final study to be mentioned is one by Gallagher, Sanders-Bush, and Sulser (1972) in which they used lower, and they claim more realistic, doses of THC in rats. The actual doses (5.5 mg./kg. i.p. or 1 mg./kg. i.v.) were sufficient to cause marked behavioural

changes in the animals, which displayed catalepsy, a tendency to squeal characteristically, and evidence of the analgesic effects of the drug. There were no detectable changes in either the levels of 5-HT or 5-HIAA in the forebrain or the brain-stem, or in the rate of turnover of cerebral 5-HT.

These examples suffice to show the confusion in the literature concerning the effects of cannabinoids on levels of brain amines. One possible conclusion is that effects are only seen after large doses and are, therefore, non-specific. However, Truitt and Anderson (1971) carefully surveyed all the evidence and reached the conclusion that cannabis extracts and Δ^9 -THC, in common with other hallucinogens such as LSD, mescaline, and phencyclidine, caused significant increases in brain 5-HT levels while producing slight falls or having no effect on noradrenaline levels. This conclusion, however, may be a premature attempt to fit the cannabinoids into the overall picture, and more work is clearly required to decide whether they have a common or different mode of action to the sympathomimetic hallucinogens.

IV. GENERAL CONCLUSIONS

A great deal remains to be learned concerning the modes of action of hallucinogenic agents. It is abundantly clear that the three main classes, the sympathomimetic amines, the antiacetylcholine drugs, and the cannabinoids, produce effects which are only superficially similar and which may well be mediated through different mechanisms. The best evidence currently available suggests that the sympathomimetic amines compete with 5-HT for receptors while the antiacetylcholine drugs compete with acetylcholine. Whether these are the only, or even the major, components in their mechanisms of action remains to be determined. Both of these classes of drugs give rise to central nervous system excitation, which suggests an inhibitory role for the transmitters with which they apparently compete. Cannabinoids, on the other hand, produce a depression of the central nervous system, but whether this results from a direct action or is mediated through chemical transmitters is not known. The effects produced by hallucinogenic drugs remain as mysterious as the mechanisms by which the body and mind reacts to mediate them.

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